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THE FAILURE OF ANTIHISTAMINIC DRUGS TO PREVENT OR CURE THE COMMON COLD AND UNDIFFERENTIATED RESPIRATORY DISEASES*

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THE value of the antihistaminic drugs in the treatment and prevention of the common cold and undifferentiated respiratory diseases has been investigated as follows: by observation of the effect of the drugs in naturally occurring respiratory infections; and by determination of the influence of the drugs on the occurrence and subsequent course of common colds developing after the experimental inoculation of normal volunteers. In neither type of study have the drugs proved to be effective. The procedures employed and the results obtained in the two studies are presented below under separate headings.

Use of Antihistaminic Drugs in Naturally Occurring Respiratory Infections in Families

For the past two years the occurrence of illnesses has been continuously observed in a population of families.[1] During December, 1949, and January, 1950, the voluntary use of antihistaminic drugs by members of some of these families provided an opportunity to assess the therapeutic value of the drugs under well defined circumstances.

Methods

Observation of illnesses. The general procedures employed for the study of illnesses in these families have been presented elsewhere.[1] The following features, however, were pertinent to the present study: a complete medical history had been obtained from each person at time of admission to the study; for each family member a daily record of the presence or absence of symptoms was made in the home, usually by the mother; the families were asked to notify the Department of Preventive Medicine at the onset of any illness, no matter how minor, and in most cases one of three physicians from the Department visited the home at least once to characterize that illness by history and physical examination; white-cell counts and roentgenograms of the chest were obtained when bacterial infection or pneumonia was suspected; and each week the family was visited by a field worker, who checked the records and interrogated the family to determine the progress of existing illnesses and to detect the presence of any unreported illness. Cultures of the pharynx were obtained from each person at weekly intervals as well as at the onset of each illness. *Beta*-hemolytic streptococci and pneumococci, when present, were identified in cultures made at the time of illness. Pharyngeal swabs were collected in broth from approximately three fourths of the patients and were examined for the presence of the influenza viruses by intra-amniotic inoculation of chick embryos.

During November, 1949, a number of the families began to take antihistaminic drugs for the treatment of respiratory illnesses. Accordingly, on November 28, 1949, the following letter was mailed to each family:

> Recent publicity in the newspapers, over the radio and through pharmaceutical advertising, is advocating the use of the so-called "antihistamine" drugs for the treatment and prevention of common colds. We in the Department have no fixed opinion as to their effectiveness, although we feel that the results thus far published do not prove that the drugs are true remedies. We do not wish either to encourage or discourage their use. If you do use one of these drugs, however, we would like to know when such medication is taken, so that at a later date we may be better able to evaluate the records of your illnesses.

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Would you please note on your charts the names and amounts of such drugs as each member of your family may use?

Beginning on December 1, 1949, the field workers checked each person's record for completeness of information regarding the use of any antihistaminic drug.

Diagnosis. The cases of respiratory disease on which the subsequent analyses are based were classified as follows:

Common cold. An acute respiratory illness characterized by symptoms and physical signs referable predominantly to the nasal passages (rhinorrhea, sneezing and nasal obstruction), with or without such symptoms as fever, lacrimation, irritation of the throat, hoarseness and cough. The duration of such illnesses varied from less than twenty-four hours to more than seven days. This category thus includes mild, moderate and severe common colds.

Undifferentiated respiratory diseases:

Questionable respiratory disease (?RD). The occurrence of a single symptom, such as rhinorrhea, sneezing, irritated throat or cough, for periods varying from less than one day to several days.

Acute respiratory disease (ARD). An acute respiratory illness characterized by prominence of symptoms and signs referable to the throat and lower respiratory tract with or without involvement of the nasal passages. Fever and constitutional symptoms are usually present, but may be absent. This disease may differ etiologically from the common cold.[2]

"Obscure" respiratory disease. An acute respiratory illness differing in its characteristics from the above groups sufficiently to require separate classification.

Illnesses diagnosed as bacterial infections (streptococcal tonsillitis and pharyngitis, pneumococcal pneumonia and so forth), nonstreptococcal exudative tonsillitis and pharyngitis[1, 3] and primary atypical pneumonia were excluded from the present analysis.

There were no cases of hay fever or allergic rhinitis recognized as such during the two months of the study. Asthma occurred twice — once in conjunction with a respiratory infection.

Influenza virus was not isolated from any patient, nor was epidemic influenza recognized in the population of Cleveland during the study.

The diagnosis of each respiratory illness was made by the physician observing the patient and was based on the combined data afforded by the family's records, the physician's observations, the field worker's reports and the results of pharyngeal cultures and special examinations. Uniformity of diagnosis was sought by a review of all records by one physician; any disagreement in diagnosis was resolved by discussion after re-evaluation of the illness. This is the same procedure that has been employed during the past two years for the diagnosis of illnesses occurring in the families. The physicians were aware of the use of the antihistaminic drugs in the individual illnesses since statements to that effect were present on the patients' records.

Analysis. Pertinent data regarding each illness, such as age, diagnosis, date of onset, medication and duration of symptoms, were transferred to punch cards for analysis. Duration of illness was defined as the interval, expressed as whole calendar days, from the day of onset to the last day of occurrence of any respiratory symptom. The duration was determined objectively by direct transfer of the information from the patient's record. In an occasional illness a decision by the reviewing physician was necessary to determine whether or not the occurrence of new symptoms constituted a new illness or was part of a preceding or subsequent illness. The decision was based not only on the patient's record but also on the notes of the observing physician and the field worker. This procedure had also been employed during the preceding two years and was not altered for purposes of the present study.

Analyses by age were carried out because of age differences in the frequency and duration of respiratory illnesses, and also because children under the age of six years were rarely given the antihistaminic drugs. Comparisons of the effect of the drugs are therefore made on the basis of age-specific rates for adults, children six years of age and over and children under the age of six years, rather than by the total rates of the treated and untreated groups.

Allergy of the respiratory tract was determined by a review of the past history and of the episodes of illness occurring in each person since his admission to the family study. A history of hay fever, allergic rhinitis or asthma, or an observed illness so diagnosed, was accepted as evidence sufficient to place the person in the category of "respiratory allergy."

Types of drugs and adequacy of dosage. In almost all cases the drugs employed were purchased over the counter and were used in single doses of 25 mg. or equivalent amounts. The number of illnesses in which each drug was used is given in Table 1.

There was considerable individual variation in the dosage of antihistaminic drugs taken, and some variation in the promptness with which medication was started after the appearance of the first symptom. The following definitions were therefore adopted:

"Adequate" dosage: three or more doses taken, with medication beginning on the same calendar day as the onset of the first symptom; each dose equivalent to 25 mg. or more for adults and 10 mg. or more for children.

(b) "Inadequate" dosage: less than three doses taken, or medication started on the second calendar day of symptoms or thereafter.

(c) No antihistaminic medication.

Results

During the two-month period of observation, 376 respiratory illnesses occurred in 203 of the 253 persons comprising the 55 families. Eighty-seven illnesses were treated with antihistaminic drugs, and 289 were not so treated. Clinical classification showed that three fourths of both the treated and control illnesses were compatible with a diagnosis of the common cold (Table 2). The remaining undifferentiated respiratory illnesses were likewise proportionately divided, except for the 5 cases of "obscure" illness. These 5 illnesses occurred in children under the age of six years; one was of a single day's duration, the others were of seven or more days' duration. With this exception, the age-specific occurrence of the treated and control illnesses was similar (Table 3). Such comparability permits the direct comparison of the treated and control illnesses with respect to the effect of the drugs on the illnesses. Furthermore, it indicates that the administration of the drugs did not alter the clinical picture sufficiently to influence the pattern of diagnostic classification.

Consideration of the allergic background showed that approximately a fifth of the illnesses occurred in persons who had histories of "respiratory allergy" and that more than a third of these illnesses were treated with antihistaminic drugs (Table 4). In contrast, slightly less than a fifth of the illnesses in the "nonallergic" persons were so treated. This tendency held true for all age groups. The difference between the treated and control illnesses is in a direction that should weight a comparison of them in favor of a beneficial effect from the use of the drugs if some of the illnesses had been allergic rather than infectious. Analysis of the duration of the illnesses in patients with an allergic background, however, showed that both their treated and untreated illnesses were of the same duration.

Comparison of the duration of all treated and control illnesses (Table 5) shows that the antihistaminic drugs had no beneficial effect, regardless of whether the dosage was "adequate" or "inadequate." Similarly, no benefit was seen in the common cold (Table 6) or in the other undifferentiated respiratory illnesses (not shown in tabular form, but the data may be obtained by subtraction of the figures in Table 6 from those in Table 5). Likewise, the duration of

TABLE 1. *Antihistaminic Drugs Used in Naturally Occurring Respiratory Infections.*

DRUG	TRADE NAME	NO. OF ILLNESSES
Thonzylamine hydrochloride	Anahist, Neohetramine, Resistabs	55
Chlorprophenpyridamine maleate	Chlor-Trimeton, Coricidin	13
Tripelennamine hydrochloride	Pyribenzamine	8
Diphenhydramine hydrochloride	Benadryl	3
Prophenpyridamine	Inhiston	3
Chlorcyclizine hydrochloride	Perazil	1
Pyranisamine maleate	Neo-Hist	1
More than one drug		2
Unknown		1
Total		87

TABLE 2. *Clinical Classification of the Treated and Control Illnesses.*

DIAGNOSIS*	TREATED ILLNESSES	CONTROL ILLNESSES	ALL ILLNESSES
Common cold	66 (75.9%)	218 (75.4%)	284 (75.5%)
Undifferentiated respiratory diseases:			
? RD	16 (18.4%)	40 (13.8%)	56 (14.9%)
ARD	5 (5.7%)	26 (9.0%)	31 (8.2%)
"Obscure"	0	5 (1.7%)	5 (1.3%)
Totals	87 (100.0%)	289 (99.9%)	376 (99.9%)

*Diagnostic categories defined in text.

TABLE 4. *Proportion of Illnesses Treated with Antihistaminic Drugs According to History of "Respiratory Allergy."*

HISTORY OF "RESPIRATORY ALLERGY"	TOTAL NO. OF ILLNESSES	TREATED ILLNESSES
Present	82	30 (36.6%)
Absent	294	57 (19.4%)
Totals	376	87 (23.1%)

TABLE 3. *Age-Specific Occurrence of the Treated and Control Illnesses.*

DIAGNOSIS*	ILLNESSES AMONG ADULTS		ILLNESSES AMONG CHILDREN UNDER SIX YEARS		ILLNESSES AMONG CHILDREN SIX YEARS AND OVER	
	TREATED	CONTROL	TREATED	CONTROL	TREATED	CONTROL
Common cold	39 (72.2%)	54 (72.0%)	13 (81.3%)	112 (74.2%)	14 (82.4%)	52 (82.5%)
Undifferentiated respiratory diseases:						
? RD	10 (18.5%)	12 (16.0%)	3 (18.7%)	19 (12.6%)	3 (17.6%)	9 (14.3%)
ARD	5 (9.3%)	9 (12.0%)	0	15 (9.9%)	0	2 (3.2%)
"Obscure"	0	0	0	5 (3.3%)	0	0
Totals	54	75	16	151	17	63

*Diagnostic categories defined in text.

nasal symptoms was not abbreviated by the antihistaminic drugs (Table 7). Moreover, no beneficial effect of the drugs could be shown when "adequate" dosage was defined as eight or more instead of three or more doses.

Table 5. *Duration of All Treated and Control Respiratory Illnesses.*

Duration of Illness	No. of Adults				No. of Children under Six Years				No. of Children Six or More Years			
	Treated			Control	Treated			Control	Treated			Control
days	*adequate dosage*	*inadequate dosage*	*total*		*adequate dosage*	*inadequate dosage*	*total*		*adequate dosage*	*inadequate dosage*	*total*	
1–2	6(20.7%)	4(16.0%)	10(18.5%)	15(20.0%)	1(25.0%)	3(25.0%)	4(25.0%)	19(12.6%)	3(33.3%)	2(25.0%)	5(29.4%)	14(22.2%)
3–6	9(31.0%)	7(28.0%)	16(29.6%)	22(29.3%)	0	2(16.7%)	2(12.5%)	29(19.2%)	4(44.4%)	3(37.5%)	7(41.2%)	22(34.9%)
7+	14(48.3%)	14(56.0%)	28(51.9%)	38(50.7%)	3(75.0%)	7(58.3%)	10(62.5%)	103(68.2%)	2(22.2%)	3(37.5%)	5(29.4%)	27(42.9%)
Totals	29	25	54	75	4	12	16	151	9	8	17	63

Finally, comparison of the duration of treated and untreated illnesses in the same person should eliminate the factor of individual variation in the response to respiratory infection. Thirty-two patients had two or more respiratory illnesses during the period of observation, at least one of which was treated and one or more was not treated (Table 8). Again, it was impossible to detect a significant difference between the durations of the treated and untreated illnesses.

Table 6. *Duration of the Treated and Control Common Colds.*

Duration of Illness	No. of Adults				No. of Children under Six Years				No. of Children Six or More Years			
	Treated			Control	Treated			Control	Treated			Control
days	*adequate dosage*	*inadequate dosage*	*total*		*adequate dosage*	*inadequate dosage*	*total*		*adequate dosage*	*inadequate dosage*	*total*	
1–2.....	3(13.0%)	0	3 (7.7%)	10(18.5%)	1(25.0%)	0	1 (7.7%)	6 (5.4%)	2(28.6%)	1(14.3%)	3(21.4%)	7(13.5%)
3–6.....	7(30.4%)	7(43.8%)	14(35.9%)	16(29.6%)	0	2(22.2%)	2(15.4%)	23(20.5%)	3(42.9%)	3(42.9%)	6(42.9%)	20(38.5%)
7+.....	13(56.5%)	9(56.2%)	22(56.4%)	28(51.9%)	3(75.0%)	7(77.8%)	10(76.9%)	83(74.1%)	2(28.6%)	3(42.9%)	5(35.7%)	25(48.1%)
Totals	23	16	39	54	4	9	13	112	7	7	14	52

Table 7. *Duration of Nasal Symptoms in All Treated and Control Illnesses.**

Duration of Symptoms	No. of Adults				No. of Children under Six Years				No. of Children Six or More Years			
	Treated			Control	Treated			Control	Treated			Control
days	*adequate dosage*	*inadequate dosage*	*total*		*adequate dosage*	*inadequate dosage*	*total*		*adequate dosage*	*inadequate dosage*	*total*	
1–2	5(17.2%)	5(20.0%)	10(18.5%)	16(21.3%)	1(25.0%)	3(25.0%)	4(25.0%)	15 (9.9%)	4(44.4%)	1(12.5%)	5(29.4%)	13(20.6%)
3–6	8(27.6%)	5(20.0%)	13(24.1%)	19(25.3%)	1(25.3%)	2(16.7%)	3(18.8%)	31(20.5%)	2(22.2%)	4(50.0%)	6(35.3%)	21(33.3%)
7+	12(41.4%)	11(44.0%)	23(42.6%)	32(42.7%)	2(50.0%)	7(58.3%)	9(56.2%)	98(64.9%)	2(22.2%)	2(25.0%)	4(23.5%)	24(38.1%)
No nasal symptom..	4(13.8%)	4(16.0%)	8(14.8%)	8(10.7%)	0	0	0	7 (4.6%)	1(11.1%)	1(12.5%)	2(11.8%)	5 (7.9%)
Totals	29	25	54	75	4	12	16	151	9	8	17	63

*The duration of nasal symptoms (sneezing, nasal discharge or obstruction) was defined as the inclusive number of calendar days from the onset to the last day of occurrence of any such symptom.

It is concluded from these data that the antihistaminic drugs, as their use was observed in this population, were ineffective as therapeutic agents for the common cold and other undifferentiated respiratory illnesses.

Effect of Antihistaminic Drugs on Common Colds Developing After Inoculation of Volunteers

The second study was designed to evaluate the prophylactic and therapeutic effect of two antihistaminic drugs, Pyrrolazote and Neohetramine, on the occurrence and subsequent course of common colds developing after the experimental inoculation of normal volunteers.

Methods

Inoculum. The inoculum consisted of nasal secretions and washings from a single donor who had a typical severe common cold beginning on October 24, 1948. The illness was characterized by sneezing, nasal obstruction, profuse watery nasal discharge, hoarseness and headache. There was no fever. The acute symptoms lasted for five days and were followed by a period of approximately two weeks during which there were thick nasal discharge, cough and

sputum. The secretions were collected on the second day of illness when nasal discharge was profuse and serous; they were diluted 1:10 in sterile skimmed milk, frozen at –76° C. and stored at –20° C. Cultures on horse-blood agar, sheep-blood agar, and Loeffler's medium and the intraperitoneal inoculation of mice yielded only *Staphylococcus aureus* in small numbers.

The inoculum had been shown to be infectious in two experiments in volunteers performed for another purpose; in both experiments approximately 60 per cent of those inoculated developed definite colds.

For the first experiment in the present study (December 14, 1949), the inoculum was a 1:10 dilution of the nasal secretions. Part of this pool was refrozen and stored at –70° C. until the second experiment (February 13, 1950), at which time additional sterile skimmed milk was added to make a final dilution of 1:20. Sterile skimmed milk was employed as a control inoculum in the second experiment.

Antihistaminic drugs and placebos. Pyrathiazine hydrochloride (Pyrrolazote*),[4] in doses of 50 mg. four times daily, was employed in the first experiment; an inert placebo* served as the control drug. Administration was started two hours before inoculation and was continued for five days.

Thonzylamine hydrochloride (Neohetramine†), in doses of 50 mg. four times daily, was employed in the second experiment; an inert placebo,† indistinguishable in appearance, served as the control drug. Administration was started so that three doses were taken before inoculation and was continued for five days.

Conduct of experiments. Volunteers in the first experiment consisted of 12 medical students and 6 members of the staff. The 31 volunteers in the second experiment were medical students. Only persons who had been free from colds for at least two weeks were accepted, and most had not had a cold for a considerably longer period. A history and local physical examination excluded volunteers with chronic respiratory symptoms. Grouping of the volunteers to receive nasal secretion, sterile milk, the antihistaminic drug or the placebo was made on the basis of numbers assigned at random.

The volunteers were given the inoculum by dropping of 0.25 cc. into each nostril. So far as possible the inoculum was retained in the nose or nasopharynx for ten minutes. The volunteers then pursued their usual activities and kept daily records of their symptoms on forms provided them. Each volunteer was interviewed daily for at least six days by a physician who separately recorded the symptoms and examined the upper respiratory tract. Illnesses developing later than six days after inoculation were excluded from consideration.

*Kindly supplied by the Upjohn Company, Kalamazoo, Michigan.
†Kindly supplied by Wyeth, Incorporated, Philadelphia, Pennsylvania.

The volunteers were bled at the beginning of the experiments and two or three weeks later. Paired serums were examined for antibodies to the influenza viruses (PR8, FM1 and Lee strains) by the agglutination-inhibition test. No fourfold or greater increases in titer were found. Pharyngeal cultures obtained at the time of inoculation revealed no important respiratory pathogens.

Analysis of results. The daily records of the volunteers and of the physicians were employed for evaluation of the illnesses. The following clinical classification was employed:

Definite cold: defined by the criteria given above for the diagnosis of the common cold occurring naturally in families.

Questionable mild cold: presence of a symptom or symptoms, usually nasal stuffiness, slight throat symptoms or slight headache, without definite physical signs.

No cold: no respiratory symptoms over and above those usually experienced by the subject.

The nature of the observations permitted the subdivision of definite colds on the basis of severity of certain symptoms, as follows:

Mild cold: definite but mild symptoms of a cold, with no constitutional reaction.

Moderate cold: considerable nasal discharge, irritated throat and sometimes cough, headache and mild constitutional symptoms.

Severe cold: profuse nasal discharge, marked nasal obstruction, definite or severe constitutional symptoms.

Questionable mild colds were considered as "no cold" for the purposes of the study.

Classification was made independently by two physicians, who compared their results, resolved any differences and recorded the final decision without knowledge of the nature of the inoculum or medication received by the volunteer. The question of whether or not an illness should be classified as a definite cold required a compromise decision only once. In this case, one physician changed his in-

TABLE 8. *Duration of Treated and Untreated Illnesses Occurring during the Period of Observation in the Same Patients.*

Duration of Illness	No. of Treated Illnesses						No. of Untreated Illnessess	
	"Adequate" dosage		"Inadequate" dosage		Total			
days								
1–2	3	(18.8%)	6	(23.1%)	9	(21.4%)	8	(19.5%)
3–6	5	(31.3%)	6	(23.1%)	11	(26.2%)	10	(24.4%)
7+	8	(50.0%)	14	(53.8%)	22	(52.4%)	23	(56.1%)
Totals ...	16	(100.1%)	26	(100.0%)	42	(100.0%)	41	(100.0%)

dependent diagnosis from questionable mild cold to a final diagnosis of mild cold.

Incubation period was the elapsed time between inoculation and appearance of the first symptom. The duration of a cold was taken as the number of calendar days from onset of illness to the disappearance of abnormal symptoms. The duration of a particular symptom was the number of calendar days on which the symptom was present.

Results

Occurrence of illnesses. The administration of antihistaminic drugs in doses of 50 mg. four times a day failed to prevent the development of colds, despite the fact that medication was started before inoculation and was continued for several days thereafter (Tables 9 and 10). In the first experiment there were equal numbers of definite colds in the groups that received the antihistaminic drug and the placebo, respectively. In the second experiment there were 6 definite colds in the treated group and 3 definite colds in the placebo group. Eleven volunteers in the second experiment were inoculated with sterile milk; 3 developed colds; 2 of these were taking the antihistaminic drug.

Severity of illness, duration of symptoms and length of incubation periods. The antihistaminic drugs had no favorable effect on the severity of the illnesses, the duration of symptoms or the length of the incubation periods (Table 11).

Duration of nasal symptoms, throat symptoms and cough. No appreciable differences in the duration of nasal symptoms, throat symptoms or cough were found in the 14 colds treated with the antihistaminic drugs in comparison to the 10 colds treated with placebos (Table 12).

TABLE 9. *Occurrence of Common Colds According to the Type of Inoculum and Medication with Antihistaminic Drugs and with Placebos.*

MEDICATION	VIRUS AS INOCULUM*				STERILE MILK AS INOCULUM			
	NO. INOCULATED	RESULT†			NO. INOCULATED	RESULT†		
		+	±	0		+	±	0
Experiment I:								
Pyrrolazote, 50 mg. 4 times daily ...	9	6‡	1	2	§	§	§	§
Placebo	9	6	2	1	§	§	§	§
Experiment II:								
Neohetramine, 50 mg. 4 times daily	10	6	2	2	4	2	1	1
Placebo	10	3	1	6	7	1	0	6

*Dilution 1:10 in Experiment I and 1:20 in Experiment II.

†Results expressed as follows:
+ = definite cold — mild, moderate or severe;
± = questionable mild cold;
0 = no cold.

‡One of these volunteers had symptoms of a cold beginning on the day of inoculation.

§Not done.

Occurrence of colds in the milk-inoculated groups and in the population. In the first experiment (Table 9), volunteers were not given a sterile inoculum to test the frequency of occurrence of naturally acquired colds. During the period of the experiment an epidemic of colds was not in progress in the population from which the volunteers were drawn.

In the second experiment (Table 9), 11 volunteers were inoculated with sterile milk, and 3 subsequently developed colds. The other 8 subjects had no abnormal symptoms. A questionnaire survey of the rest of the class of 80 students revealed that 12 of them developed colds during the first six days of the experiment. Thus, an epidemic of natural colds was occurring during the second experiment.

Side reactions. In the first experiment 2 volunteers noted mild diarrhea; both had received the placebo. In the second experiment 2 volunteers noted mild diarrhea, and both had received Neohetramine; of 4 volunteers reporting drowsiness, 2 had received Neohetramine, and 2 had received the placebo.

Regularity and identity of medication. At the end of the experiments the volunteers were questioned regarding the tablets they had received. Forty-two had taken the tablets on schedule; 5 had failed to take one dose, and 2 had failed to take two doses on schedule. Of these 7, 4 had received antihistaminic drugs, and 3 had received placebos. The volunteers in the second experiment were also asked whether they had received an antihistaminic drug or a placebo; 27 were not able to identify their medication; 3 had noted a bitter taste and believed correctly that they were receiving the antihistaminic drug; 1 believed he was receiving the placebo because it was not bitter. Only 1 of these 4 developed a cold, and he had taken the antihistaminic drug.

TABLE 10. *Occurrence of Common Colds According to the Type of Inoculum and Medication with Antihistaminic Drugs and with Placebos (Combined Results of Experiments I and II).*

MEDICATION	VIRUS AS INOCULUM				STERILE MILK AS INOCULUM			
	TOTAL INOCULATED	+*	±	0	TOTAL INOCULATED	+	±	0
Antihistamine	19	12	3	4	4	2	1	1
Placebo	19	9	3	7	7	1	0	6

*+ = definite cold;
± = questionable mild cold;
0 = no cold.

DISCUSSION

An evaluation of antihistaminic drugs for the prevention and treatment of the common cold and other undifferentiated respiratory diseases has been attempted in a population of families and in normal volunteers. No beneficial effect of these drugs has been found. These results are in contrast to pre-

vious reports,[5-10] which have recently been reviewed in detail by the Council on Pharmacy and Chemistry of the American Medical Association.[11]

The families under study by the Department of Preventive Medicine for the past two years provided a logical population in which to observe voluntary use of the antihistaminic drugs. Procedures had been developed to observe and characterize the illnesses in this population, and the same methods could be used for this purpose. Although it was not possible to withhold the knowledge of the use or lack of use of the drug from the physicians diagnosing the individual illnesses in this study, the distribution of illnesses by diagnosis strongly indicates that bias did not affect the diagnostic classification (Tables 2 and 3). The duration of illness could be determined objectively from the families' records. If subjective bias entered into the evaluation of the drug, therefore, it should have favored a beneficial effect, since Diehl, Baker and Cowan[12] have shown that any therapy, whether "specific" or placebo, favors a beneficial interpretation by the patient. The fact that the treated and untreated illnesses showed no differences in duration indicated the consistency and reliability of the families' records, and suggested that no advantage would be gained by continuing the study with the addition of a "placebo" group.

The type or brand of antihistaminic drug employed probably did not affect the results, since the pharmacologic action of this group of drugs is similar.[11] "Adequacy" of dosage can be surmised only from the published reports claiming a beneficial effect. Presumably three or more doses, equivalent to 25 mg. or more, beginning on the day of onset of symptoms, should be "adequate" to effect a cure.[10] In the present study, that dosage was ineffective, as was the larger amount of eight or more doses.

The second type of study, that of the inoculation of normal volunteers, had several advantages. The study was objective since it could be made under such conditions that neither the participants nor the observers were aware of the identity of either the inoculum or therapy in any given person until the final result had been appraised. The selection of subjects to receive either the drug or the placebo could be made at random, and the amount of medication and the time of its administration could be controlled. A predictable number of colds could be expected to result within a short time of inoculation. Finally, the occurrence of naturally acquired colds could not interfere with the interpretation of the results since the volunteers were receiving medication and were free from recognizable infections at the time of inoculation.

The disadvantage of small numbers, inherent in most volunteer experiments, is negated to a considerable extent by the fact that both experiments gave the same results, within the expected limits of variation. It is, of course, possible that the strain of virus used for inoculation was peculiarly resistant

TABLE 11. *Severity of Illness, Duration of Symptoms, and Incubation Periods (Combined Results of Experiments I and II).*

MEDICATION	SEVERITY OF ILLNESS				DURATION OF SYMPTOMS IN DAYS								INCUBATION PERIODS IN HOURS				
	SEVERE	MODERATE	MILD	TOTAL	2	3	4	5	6	7	7+	TOTAL	<24	25–48	49–72	73–96	TOTAL
Antihistamine ...	2	9	3	14	1	1	3	2	1	3	3	14	4*	9*	1		14
Placebo	2	6	2	10		1	3	1	1	1	3	10	1	5	3	1*	10

*One of the subjects in each of these three groups developed a common cold after inoculation with sterile milk.

TABLE 12. *Duration of Specific Symptoms (Combined Results of Experiments I and II).*

SYMPTOM	MEDICATION	DURATION OF SYMPTOM IN DAYS									TOTAL NO. OF CASES
		0	1	2	3	4	5	6	7	7+	
Any nasal symptom	AH*			1	2	4	2	1	1	3	14
	Placebo			1	2	2	3		1	1	10
Sneezing	AH	2	3	3	4	2					14
	Placebo	1	1	4	1	1	2				10
Nasal obstruction	AH		1		5	3	2	1	1	1	14
	Placebo	1	1	2	2	1	2			1	10
Nasal discharge	AH		1		2	4	4		1	2	14
	Placebo			2	4	3				1	10
Irritated or sore throat...	AH	4	3	3	1	2		1			14
	Placebo	2	2	3	1	2					10
Cough	AH	6		1	1	3	2	1			14
	Placebo	6	2			1		1			10

*Antihistaminic drug.

to any effect that the antihistaminic drugs might have. Such a conclusion appears to be unlikely in view of the results obtained in the family study. Moreover, the drug was apparently without effect in the two infections — presumably due to naturally occurring strains of virus — that developed less than twenty-four hours and thirty hours, respectively, after inoculation of sterile milk.

The quantity of virus contained in the inoculum given each volunteer was not determined, but was estimated to have been approximately five to ten 50 per cent infective doses on the basis of data obtained by Andrewes[13] in similar studies. Such a dose of virus does not appear to offer an explanation for the failure of the antihistaminic drugs to prevent or alter the course of the resulting colds. The virus of the common cold may be present in nasal secretions twenty-four hours before the onset of symptoms and is present in large quantities at the time of onset.[13] In comparison, the dose of virus employed in the present study must have been extremely small. If the antihistaminic drugs have any effect when taken at the first sign of a cold, they should have had even more effect at the time of inoculation of the volunteers.

The results of the volunteer study clearly show that the antihistaminic drugs had no effect on the occurrence, severity or symptomatology of common colds developing under conditions that might reasonably be expected to reveal a marked effect if these agents were specific remedies.

Summary

The antihistaminic drugs have been evaluated by observation of their effect on naturally occurring respiratory infections and by determination of their influence on the occurrence and subsequent course of common colds developing after the experimental inoculation of volunteers. No beneficial prophylactic or therapeutic effect was demonstrated.

We gratefully acknowledge the contributions of the families, the medical students and the other persons who volunteered or in other ways took part in this study, and of Dr. Robert F. Parker and Dr. Morris Tager for assisting in the inoculation of the volunteers.

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SOLITARY AND MULTIPLE ADENOMATOUS POLYPS OF THE GASTROINTESTINAL TRACT*

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EIGHTY-FIVE consecutive cases of solitary and multiple adenomatous polyps of the gastrointestinal tract at the Boston City Hospital have been reviewed.

Solitary polyps were noted in 58 and multiple polyps in 27 cases. The ratio of solitary to multiple polyps was 2:1. Males were affected twice as often as females. Most of the polyps became manifest after the age of forty (62 cases). Eleven cases were observed in children under ten years of age, of whom 9 had solitary and 2 multiple polyps in the rectum. Dixon[1] has observed 2 infants, each eighteen months of age, afflicted with multiple polyposis. These are probably the youngest patients with this disease recorded in the literature. Four of our cases occurred in children two years old, of whom 3 had solitary and 1 multiple polyps. Gass[2] has stated that no infant has ever been born with polyps of the gastrointestinal tract. Some investigators claim that a nidus of a polyp is present at birth even though it cannot be detected, but this concept has no proof to substantiate it.

LOCATION

Helwig[3] studied the incidence and distribution of benign tumors of the colon and rectum in 1400 autopsies and recorded all grossly observable mucosal elevations. He found 154 benign tumors and recorded their incidence and type as follows: adenomas, 139; lipomas, 13; leiomyoma, 1; and carcinoid, 1. Of the 139 adenomas, 80 were of the solitary type, and 59 were of the multiple variety. Approximately 50 per cent of the patients with rectal adenomas were also found to have adenomas in the colon. The adenomas were located as follows: cecum, 11.8 per cent; ascending colon, 15.4 per cent; hepatic flexure, 4. 4 per cent; transverse colon, 11.8 per cent; descending colon, 8.1 per cent; sigmoid, 27.9 per cent; and rectum, 15.8 per cent.

The frequency with which the various anatomic segments were involved with polyps in the 85 cases at the Boston City Hospital was recorded as follows: stomach, 10; duodenum, 1; ileum, 1; ascending colon, 3; transverse colon, 6; descending colon, 7; sigmoid, 5; and rectum and rectosigmoid, 69 cases.

The distribution of the 58 solitary polyps was as follows: stomach, 7; ileum, 1; descending colon,1; and rectum and rectosigmoid, 49. In the 27 multiple cases the stomach was involved in 3, the duodenum in 1, the ascending colon in 3, the transverse colon in 6, the descending colon in 6, the sigmoid in 5, and the rectum and rectosigmoid in 20 cases. Fifty per cent of the patients with multiple polyps in the rectum and rectosigmoid had polyps in the colon.

RECTOCOLONIC POLYPS

Rectocolonic polyps were present in 74 cases, or 87 per cent of the total cases with polyps. The location of the polyps in the rectum was noted in 56 cases as follows: posterior wall, 26; anterior wall, 15; lateral walls, 10; and diffuse, 5 cases. The posterior wall of the rectum appeared to be the wall most frequently involved with polyps.

The presenting symptoms of polyps in the rectocolon were blood in the stool (44 per cent), pain at stool (14 per cent), prolapse of rectal polyps (12 per cent) and multiple symptoms (30 per cent). The symptoms in order of their frequency were: rectal bleeding, rectal pain, diarrhea, tenesmus, prolapse of a rectal polyp, feeling of fullness in the rectum, streaks of mucus in stools, weight loss and abdominal distention.

On digital examination of the rectum, one or more polyps were palpated in 36 cases (50 per cent). A polyp was visualized by sigmoidoscopy in 56 cases, or 75.6 per cent. Fifty per cent of these 56 patients had a polyp demonstrable by barium enema. Sigmoidoscopy and digital palpation appeared to be more accurate diagnostic aids than barium enema for determining the presence of rectal or rectosigmoid polyps.

It is a well known fact that adenomatous polyps may undergo malignant transformation.[4, 5] The criteria set forth for establishing a diagnosis of malignant degeneration of a polyp were as follows: invasion of the bowel wall; infiltration of the pedicle of the polyp; blood-vessel penetration; and perineural lymphatic extension. The last two criteria are rarely found with adenomatous polyps. Atypical proliferations of the epithelial elements of the polyp, with or without mitosis, but without bowel-wall or pedicle invasion or blood-vessel or perineural lymphatic infiltration, were called premalignant lesions. Neither the size of a polyp nor the length of its pedicle had any relation to malignancy. A polyp 18 by 5 by 3 cm. in diameter across its head and with a pedicle 8 cm. long was proved to be benign even though it looked grossly malignant.

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In 24 cases of disseminated rectocolonic polyposis, cancer of the rectum or large bowel developed in 6, or 27.2 per cent. Multiple carcinomas were found in 2 cases; 1 patient had two separate carcinomas in the descending colon, and the other carcinomas in the transverse colon and rectosigmoid. The locations of the 8 cancers were as follows: rectosigmoid, 1 case; sigmoid, 1 case; descending colon, 3 cases; transverse colon, 2 cases; and cecum, 1 case. Other authors' figures for the incidence of cancer in multiple polyposis of the large bowel and rectum are: Hullsiek,[6] 34.6 per cent; McKenney,[7] 38.1 per cent; and Scarborough,[8] 50 per cent.

Three of the 50 solitary polyps of the rectocolon showed carcinomatous degeneration — an incidence of 6 per cent for solitary rectocolonic polyps. Two of the carcinomatous polyps originated in the rectum, and the other in the rectosigmoid. Colvert and Brown[9] believe that malignant adenomas do not result from the metaplasia of a benign adenoma, but are malignant from the start. On the other hand, Atwater and Bargen[10] state that benign adenomas are but a stage in the pathogenesis of carcinoma. Six cases of solitary polyps that showed noninvasive cell atypism microscopically were called premalignant or precancerous lesions.

There were 5 cases in which polyps were biopsied and a diagnosis of carcinoma was made. These patients were subjected to Miles resections, and the specimens of rectocolon on subsequent pathological examination were found to be benign. This represented an error in biopsy of rectal polyps of 5 per cent.

Treatment of most of the rectal and rectosigmoid polyps consisted of fulguration, snare amputation or excision. Fifteen patients were treated by major surgical procedures such as colotomy with excision of a solitary polyp (1 case), sigmoidotomy with removal of a solitary polyp (1 case), ileostomy and abdominoperineal total colectomy (2 cases), cecostomy with left colectomy (2 cases), two-stage Mikulicz resection (3 cases), Miles abdominoperineal resection (3 cases), ileotransverse colostomy with right colectomy (1 case), anterior segmental resection (1 case) and ileosigmoidostomy (1 case).

Gastric Polyps

Ten cases with gastric polyps were noted; 3 patients had multiple, and the rest solitary polyps. No particular location of the polyps in the stomach could be found. They were situated on the cardia, pylorus, greater and lesser curvatures and anterior and posterior walls. All the patients were over forty years of age. Brunn and Pearl[11] stated the youngest patient with gastric polyps to be twenty years old. More males were affected than females, the ratio being 2:1. All the patients with multiple gastric polyps were males, and 2 had an associated carcinoma of the stomach. One solitary gastric polyp was reported as carcinomatous. The incidence of gastric carcinoma in these 10 cases with gastric polyps was 30 per cent. No relation between the size of the gastric polyp (or the length of its pedicle) and malignant degeneration could be established. Brunn and Pearl[12] reported the incidence of malignant degeneration of gastric polyps to be 12 per cent whereas other authors reported the incidence as 28 per cent (Stewart[13]), 35 per cent (Miller, Eliason and Wright[14]) and 41 per cent (Benedict and Allen[15]).

The presenting symptoms of gastric polyps were dyspepsia (69 per cent), hematemesis (20 per cent) and multiple complaints (20 per cent). Symptoms in order of frequency were dyspepsia, epigastric pain, hematemesis and vomiting.

Gastrointestinal series performed in the 10 cases demonstrated polyps in 6. Gastroscopy was performed in 7 cases, in all of which polyps were visualized. Gastric analysis revealed anacidity in 2 cases, and gastric washings were guaiac positive in 2. Gastroscopy seemed to be a more accurate means for the diagnosis of polyps than x-ray examination.

Treatment consisted of gastrotomy and polypectomy for solitary polyps and subtotal gastrectomy for multiple polyps. In the 2 cases with multiple polyposis of the stomach associated with carcinoma, exploratory laparotomy showed inoperability of the gastric carcinoma.

Small-Bowel Polyps

Small-bowel polyps were observed in 2 cases. One patient had a solitary polyp in the ileum, and the other had multiple polyps in the duodenum, transverse colon and rectosigmoid.

The solitary ileal polyp was clinically characterized by the sudden onset of crampy right-lower-quadrant pain, nausea and vomiting suggestive of appendicitis. Operation revealed a 3-cm. fungating antimesenteric polyp obstructing the ileocecal valve. A segmental resection of the terminal ileum containing the polyp and an end-to-side ileoascending colostomy were performed. The case with multiple duodenal polyps demonstrated the point that if any segment of the gastrointestinal tract contains polyps, one should look for additional polyps in other segments.

Regarding malignant degeneration of these polyps, very little can be said, for very few carcinomatous small-bowel polyps have been reported in the literature. Nevertheless, small-bowel polyps should be considered as potentially malignant lesions similar to polyps in the stomach and rectocolon.[16] Roentgenographic diagnosis is often difficult. Jeghers et al.[17] recently commented on the association of melanosis of the lips with intestinal polyposis.

Summary

Eighty-five cases of solitary and multiple polyps of the gastrointestinal tract are reviewed. The ratio

of solitary polyps to multiple polyps was 2:1. Most of the polyps occurred in patients over forty years of age.

Of seventy-four patients with rectocolonic polyps, a polyp could be palpated digitally in 50 per cent, visualized through a sigmoidoscope in 75.6 per cent and demonstrated by barium enema in 50 per cent. Carcinoma of the rectum or large bowel occurred in 6 patients with disseminated rectocolonic polyps. Multiple carcinomas were present in 2 cases. Carcinomatous degeneration of a solitary rectocolonic polyp was noted in 1 patient.

Gastric polyps were found in 10 patients, occurring chiefly in men over forty years of age. Two patients with multiple polyps of the stomach were found to have an associated gastric carcinoma. Malignant transformation of a solitary gastric polyp was found in 1 case. Gastroscopy appeared to be more accurate than x-ray study in the diagnosis of gastric polyps.

Two cases of polyps in the small bowel were found, 1 with multiple polyps in the duodenum, and the other being a solitary polyp in the ileum. Patients with polyps in the small bowel should be suspected of having polyps elsewhere in the gastrointestinal tract.

All solitary and multiple adenomatous polyps of the gastrointestinal tract should be considered as precursors of carcinoma.

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TRANSMURAL MIGRATION OF INTESTINAL BACTERIA*

A Study Based on the Use of Radioactive *Escherichia coli*

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IN UREMIC patients subjected to peritoneal dialysis with a slightly hypertonic fluid[1] peritonitis due to *Escherichia coli* developed frequently in spite of meticulous sterile technic. The evidence suggested that bacteria entered the peritoneal cavity by transmural migration.[1] Preliminary experiments designed to test this assumption showed that *Esch. coli* can be recovered in small numbers from the peritoneal cavity of normal dogs after continued intraperitoneal injection of sterile irritating agents such as Monolate or gum tragacanth.[2] In uremic dogs, prolonged exposure of the peritoneum to dialyzing fluid was followed by the appearance of *Esch. coli* in pure culture or as the predominant organism in a mixed culture, containing in addition *Aerobacter aerogenes*, *Pseudomonas aeruginosa* or *Streptococcus faecalis*.[3] Since all the dogs in these experiments showed sterile cultures of blood taken at the time the bacteria were found in the peritoneal cavity, it was concluded that these organisms had reached the peritoneal cavity by transmural migration.

To test this conclusion still further, the migration of bacteria tagged with radioactive iodine¶ introduced into the gastrointestinal tract was studied.

Method

General Procedure

Peritonitis was produced by a chemical irritant in five groups of dogs. Radioactive material was administered immediately after bacteria appeared in substantial numbers in the peritoneal fluid (except Group C) in one of the following forms: (A) ionic radioactive iodine introduced into the gas-

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¶I^{131} was obtained from the United States Atomic Energy Commission.

trointestinal tract; (B) live radioactive *Esch. coli* injected intravenously; (C) live radioactive *Esch. coli* inserted before bacteria were recoverable from the peritoneal fluid; (D) live radioactive *Esch. coli* introduced into the gastrointestinal tract; and (E) dead radioactive *Esch. coli* introduced into the gastrointestinal tract. The amounts of radioactivity recovered from the washed peritoneal sediment twenty-four hours later in the various groups of experiments were compared.

Preparation of Radioactive Bacteria

Esch. coli was selected for tagging because of its predominance in the peritonitis induced by peritoneal irrigation for uremia in man[1] and in dogs.[2, 3] The same strain was used in all experiments. One loopful from a stock culture was inoculated into 5 cc. of plain broth (pH 7.2) and incubated at 37°C. for twenty-four hours. The entire volume was then added to 1 liter of similar broth, and incubated for seventy-two hours. The cloudy broth, which contained about 800 million living organisms per cubic centimeter, was centrifuged at 1500 revolutions per minute for one or two hours, or longer if necessary, until the supernatant fluid was macroscopically clear. The supernatant fluid was decanted and discarded. To remove traces of soluble protein, the sediment was washed three times by suspension in 500 cc. of sterile 0.85 per cent saline solution, followed by centrifugation. After the third washing the bacterial sediment was suspended in 20 to 30 cc. of 0.85 per cent saline solution.

In a few experiments reported below, in which the migration of dead bacteria was studied, the bacterial culture was heated in an autoclave at 15 pounds of pressure for thirty minutes (120°C.) prior to centrifuging and washing the bacterial sediment and prior to tagging. Subcultures of the autoclaved culture were always sterile.

Iodination with I^{131}

Tagging was accomplished by a method similar to that previously described for tagging plasma proteins[4, 5] and a polysaccharide.[6]* The saline suspension of *Esch. coli* was made alkaline with 2 cc. of 10 per cent sodium bicarbonate solution. To this was added a solution of radioactive iodine, prepared immediately before use as follows: to 20 cc. of potassium iodide, equivalent to 1 mg. of iodine, 2 or 3 millicuries of carrier-free sodium iodide (2 to 5 cc.) was added. Sodium nitrite (0.5 cc. of 1 per cent) was then added, followed by 3 cc. of 0.1 normal hydrochloric acid. The solution was allowed to stand a few minutes to complete oxidation to free iodine (yellow solution). A 10 per cent solution of sodium bicarbonate (1 cc.) was then added to neutralize the hydrochloric acid and the nitrous acid. The resulting pale-yellow solution was added with rapid swirling to the saline suspension of *Esch. coli* containing sodium bicarbonate. The color disappeared immediately.

The suspension of tagged bacteria was made up to 200 cc. with 0.85 per cent saline solution, and an aliquot (1 cc.) was taken as a standard for determining the total radioactivity used. The bacteria were again washed three times by centrifugation, followed by suspension in 500 cc. of 0.85 per cent saline solution. A final suspension in 30 cc. of 0.85 per cent saline solution was used in the experiments reported below. An aliquot (1 cc.) of this was taken as the bacterial standard for determining radioactivity of the bacteria. From the measured radioactivity content of the two standards, the amount of radioactive iodine attached to the bacteria was calculated and found to vary from 3 to 14 per cent (average 10 per cent).

Evidence for the viability of most of the tagged bacteria was provided in a few experiments in which aliquots of the washed bacteria were cultured. Growth was not different from controls, and the washed bacteria of the subculture contained the total radioactivity that was transferred to the subculture. Counts of viable bacteria indicated a loss from the iodination procedure of some 100,000 out of 750,000,000 per cubic centimeter.

Preparation of Dogs

Dogs weighing 5 to 10 kg. were given intraperitoneal injections once a day, according to weight, of 5 to 10 cc. of sterile Monolate (5 per cent monoethanolamine oleate). From the third day onward, peritoneal fluid was aspirated before the injection. A smear of the fluid always showed polynuclear leukocytes. The earlier cultures (on endo and agar plates) were sterile. Between the fourth and the ninth day of injections colonies of *Esch. coli* appeared. Injections of Monolate were continued for two to four days after they were first found, to increase the colonies to about 100 a plate, one loopful of the peritoneal exudate being used. This number was considered sufficient to proceed with the experiment.†

The 30-cc. suspension of radioactive bacteria was placed in the stomach via a tube in the last three groups (C, D and E) of dogs (Table 1), or was diluted with 1 liter of 0.85 per cent saline solution and injected intravenously over a two-hour period in one control group (B). In another control group (A) radioactive sodium iodide, containing the same amount of carrier iodine and the same number of millicuries of radioactive iodine used in iodinating the bacteria, was placed in a volume of 30 cc. of water and introduced by tube into the stomach. The number of bacteria killed in the stomach is not known.

*An attempt was made to tag *Esch. coli* by culture in nutrient mediums containing radioactive sodium iodide, iodotryptophane, iodotyrosine, iodoplasma proteins[4] or iodopeptone. No significant radioactivity was found in the washed bacteria after several days' growth.

†Three dogs could not be used in the experiments because in 1 *Esch. coli* was never found, and in 2 others the number of colonies never exceeded 20 on a plate. Two additional dogs were not used because a few colonies of *A. aerogenes* or *Ps. aeruginosa* were found in addition to *Esch. coli*.

Twenty-four hours later 150 to 250 cc. of 0.85 per cent saline solution was injected into the peritoneal cavity, and the dog was killed with a lethal dose of ether. The peritoneal fluid was then collected as quantitatively as possible. This fluid was in all cases very cloudy and usually a little bloody, and occasionally contained particles of fibrin. The volume of fluid recovered exceeded that of the injected saline solution by 3 to 300 cc. The fluid was centrifuged until the supernatant was clear. The sediment, which also varied in volume, consisted of leukocytes, erythrocytes, fibrin and the greater part of the bacteria present in the peritoneal cavity. There was no correlation between the volume of fluid or sediment and the number of colonies of *Esch. coli* cultured from the aspirated fluid.

Parietal and visceral peritoneum was partly covered with firmly adherent fibrin, and many adhesions between intestinal loops were present. To avoid perforating the intestine, with possible spillage of radioactive bacteria, no attempt was made to scrape off the fibrin, although it undoubtedly contained many bacteria.

Measurement of Radioactivity

The peritoneal sediment, which was washed three times with saline solution as described above for bacterial sediment, was placed in aluminum cups 3 cm. in diameter and evaporated to dryness at 37°C. for forty-eight hours. When the peritoneal sediment was excessive in volume, largely because of fibrin, aliquots were used. The dry weight of the sediment was estimated. To reduce the error due to self-absorption of beta rays, plasma was added to the standards in a volume sufficient after evaporation to approximate the dry weight of the sediment. These approximations were not always close, but since the error from self-absorption was at most 30 per cent and usually much less, correction for this error was not significant, thousandfold differences being obtained between the control and the test experiments. Furthermore, since the dry weight of the standard was always less than the dry weight of sediment, too high a count in the standard and too low an estimate of the percentage of radioactive bacteria in the sediment were obtained.

In a few experiments, in which the radioactivity of the samples was excessive, the counting chiefly of gamma rays was performed by insertion of an aluminum disk between the sample and the end window counter. Error due to self-absorption was thereby greatly reduced in such experiments.

The aliquots of the standards were further diluted so as to contain a radioactivity count roughly in the same range as that found in the peritoneal sediment. All measurements were over ten times background.

The radioactivity recovered in the peritoneal sediment, in percentage of the radioactivity present in the tagged bacteria that were administered, was given by the following ratio, multiplied by 100:

$$\frac{\text{Radioactivity of peritoneal sediment}}{\text{Radioactivity of bacterial standard} \times \text{dilution factor}}$$

The values obtained were lower than actual because, as noted, the peritoneal sediment could not be removed quantitatively, there was loss, though slight, of radioactive bacteria (intact or disintegrated into water-soluble protein) by the washing procedure and in some experiments, there was high self-absorption of beta rays from excessive dry weight of the peritoneal sediment that was not matched in the standards.

Table 1. *Results of Experiments.*

Group	Dog No.	Total Dose of Monolate Administered Intraperitoneally	Bacteriologic Findings in Peritoneal Exudate	Material Given	Radioactivity of Peritoneal Sediment
		cc.			percentage of total given
A	7	60	Heavy growth of *Esch. coli*	Radioactive iodide ion by stomach tube	0.000275
	14	65	Moderate to heavy growth of *Esch. coli*	Radioactive iodide ion by stomach tube	0.0001
B	16	80	Heavy growth of *Esch. coli*	Radioactive *living Esch. coli* intravenously	0.00174
	13	80	Heavy growth of *Esch. coli*	Radioactive *living Esch. coli* intravenously	0.006*
C	3	30	Sterile	Radioactive *living Esch. coli* by stomach tube	0.000347
	11	25	Sterile	Radioactive *living Esch. coli* by stomach tube	0.00138
D	5	35	Moderate to heavy growth of *Esch. coli*	Radioactive *living Esch. coli* by stomach tube	4.0
	6	55	Heavy growth of *Esch. coli*	Radioactive *living Esch. coli* by stomach tube	0.9
	8	40	Heavy growth of *Esch. coli*	Radioactive *living Esch. coli* by stomach tube	0.625
	1	35	Heavy growth of *Esch. coli*	Radioactive *living Esch. coli* by stomach tube	0.5
	9	70	Heavy growth of *Esch. coli*	Radioactive *living Esch. coli* by stomach tube	0.7
	10	75	Heavy growth of *Esch. coli*	Radioactive *living Esch. coli* by stomach tube	1.7
	4	35	Heavy growth of *Esch. coli*	Radioactive *living Esch. coli* by stomach tube	0.001†
E	12	95	Heavy growth of *Esch. coli*	Radioactive *dead Esch. coli* by stomach tube	1.14
	18	80	Heavy growth of *Esch. coli*	Radioactive *dead Esch. coli* by stomach tube	0.93
	17	65	Moderate to heavy growth of *Esch. coli*	Radioactive *dead Esch. coli* by stomach tube	0.074‡

*Dog died 8 hr. after injection.
†3 cc. of fluid in peritoneum; adherent fibrin not removed.
‡Dog died 6 hr. after feeding.

Results

The results are presented in Table 1. In Group A (control), in which radioactive iodide ion was fed by stomach tube after the peritoneal cavity was already yielding positive cultures of *Esch. coli*, the

washed peritoneal sediment, twenty-four hours after administration of the iodide ion, contained less than 0.0003 per cent of the radioactivity administered. In 2 dogs (Group B), in which living radioactive bacteria were given intravenously after the peritoneal cavity was already yielding positive cultures of *Esch. coli*, the washed peritoneal sediment contained 0.00174 and 0.006 per cent respectively of the radioactivity administered. The latter dog died eight hours after the intravenous injection. In Group C (control), in which living radioactive *Esch. coli* were given by tube *before* positive cultures were obtained from the peritoneal cavity (sterile chemical peritonitis), the radioactivity of the washed peritoneal sediment was 0.00138 and 0.00034 per cent respectively. The highest percentage of radioactivity obtained in the peritoneal sediment from among all dogs in groups A, B and C was 0.006.

In 6 of 7 dogs in Group D, in which living radioactive *Esch. coli* were given by stomach tube *after* the peritoneal cavity was yielding positive cultures, the washed peritoneal sediment contained from 0.5 to 4.0 per cent of the total radioactivity administered. In the seventh dog a much lower value (0.001 per cent) was found. This may have been due to the fact that a predominantly fibrinous peritonitis, with multiple adhesions and with virtually no free fluid, was present. It is not unlikely that the adherent fibrin, which was not recovered, contained a large fraction of the total radioactivity present. In 2 dogs of Group E, in which dead radioactive *Esch. coli* were given by stomach tube, *after* many colonies were being cultured from the peritoneal fluid, the washed sediment twenty-four hours after the introduction of the bacteria contained 1.14 and 0.93 per cent of the administered radioactivity. In a third dog, similarly treated, which died six hours after the radioactive bacteria had been administered, the radioactivity of the sediment was 0.074 per cent of the total given. Thus, transmural migration of dead bacteria occurred as readily as that of live bacteria.

These data show that the washed peritoneal sediment of dogs fed living or dead radioactive bacteria contains roughly a thousand times as much radioactivity as an equal amount of radioactivity administered as radioactive iodide-ion by stomach tube or as living radioactive bacteria intravenously.

Discussion

Iodination of washed bacteria with I^{131} presumably results in iodination of the bacterial protein. Whether this reaction involves the surface or the interior of the bacterial cell is not known. The quantity of carrier iodine (1 mg.) selected for the reaction with the bacterial mass from 1 liter of a seventy-two-hour culture was judged to be small enough to prevent extensive denaturation of the protein.[4, 5] That this was achieved is indicated by the persistence of viability in the labeled organisms. Disintegration of the tagged bacteria would produce soluble radioactive protein or, by further catabolic action, ionic iodide, or both. Either or both products, being soluble, would be removed by washing of the peritoneal sediment. The residual sediment, therefore, consisted of living or dead tagged and untagged bacteria, leukocytes, epithelial cells, fragments of disintegrated bacteria and cells, fibrin and insoluble proteins. If the tagged bacteria failed to enter the peritoneal cavity, one should expect no radioactivity in the peritoneal sediment or, at most, the slight amount released by bacterial metabolism or disintegration that would reach the peritoneum after general distribution to all tissues.

In the control experiments, Group A, in which ionic radioactive iodine was given by stomach tube the radioactivity content of the sediment was 0.0001 to 0.0003 per cent of the total dose administered. In the control experiments, Group B, in which living tagged bacteria were given intravenously this value was about ten times greater — that is, 0.002 to 0.006 per cent. This difference is not surprising in view of the rapid elimination of ionic iodine in the urine, and the relatively slow elimination of bacteria or their proteinaceous breakdown products. In the experiments in which the tagged bacteria were given by stomach tube before the peritoneal exudate yielded positive cultures of *Esch. coli* (Group C) the value was about the same as that for Group B — 0.002 to 0.0003 per cent. Since the values in the experiments of Groups D and E, in which both live and dead tagged bacteria were placed in the gut after the peritoneal exudate yielded positive cultures of *Esch. coli*, were about a thousand times greater than those for Groups A, B, and C — that is, from 0.5 to 4.0 per cent of the amount administered — it is proper to draw the following conclusions:

Transmural migration of *Esch. coli* into the peritoneal cavity occurs when chemical irritation of the intestinal serosa is maintained for a sufficiently long period.

The bacterial invasion of the peritoneal cavity in these circumstances is not dependent on bacterial motility, since dead and living bacteria gain entrance with equal facility.

It follows that the mechanism of invasion is a passive transfer of intestinal organisms in the current of flow across the intestinal serosa, produced by the chemical irritant.

Intravenously injected *Esch. coli* do not enter the peritoneal cavity in these circumstances in any significant quantity.

The foregoing data suggest that peritonitis in uremic patients undergoing peritoneal irrigation is due to transmural migration of *Esch. coli* and that it may be prevented by the use of antibiotics effective against intestinal flora.

Summary

A method for preparing radioactive *Escherichia coli* with radioactive iodine is described. Direct evidence of transmural migration of *Esch. coli* from the gut as a result of prolonged chemical irritation of the peritoneal cavity of the dog was provided by means of organisms tagged with radioactive iodine. Migration occurred with dead as well as with live bacteria. Invasion of the inflamed peritoneal cavity via the circulating blood was found to be insignificant.

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PERFORATION OF A GASTRIC ULCER FOLLOWING INTENSIVE RADIATION THERAPY*

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RADIATION injury of the normal gastrointestinal tract depends upon individual susceptibility as well as the dose to which the subject is exposed. Reports of lesions of the lower intestine after intensive pelvic x-ray and radium treatments are not uncommon,[1] since such therapeutic methods are frequently employed in the management of tumors of the female generative organs. Because x-ray beams are rarely concentrated on the epigastric area, serious ulceration of the stomach is seldom encountered. But Bowers and Brick[2] and Hamilton[3] have called attention to the potential intractability of the radiation-induced ulcer of the stomach when that organ is within the target area. Since acute perforation is such a striking sequel to irradiation, the following case report is submitted.

Case Report

O. M., a 29-year-old man, was examined on May 23, 1949, because of a painless enlargement of the right scrotum that had been present for 2 months. The testicle appeared to be twice the normal size, and was smooth and firm; tenderness could not be elicited, and transillumination was good. Four days later operation disclosed an enlarged, firm, irregular, right testis. The incision was extended to facilitate the removal of the mass, local lymph nodes, spermatic cord and epididymis. Microscopically, the appearance of the tissue was that of a seminoma. Intensive radiation was immediately instituted.

Between June 2 and July 8 three body areas were irradiated: the right inguinal and suprapubic (10 by 20 cm.); right epigastric (10 by 15 cm.); and right posterior lumbar (10 by 20 cm.). In each region the rays were delivered to extend beyond the midline. The treatment factors were 200 Kv., 15 ma., 0.5 mm. copper, in addition to 1-mm. aluminum filtration, with a focal distance of 50 cm. The total surface doses were 2500 r to the right suprapubic and right lumbar fields and 2750 r to the right epigastric field. During the last 10 days of radiation exposure erythema and desquamation of the right groin, diarrhea and a temporary depression of the white-cell count occurred. Three days after the completion of therapy severe diarrhea and vomiting ensued. Desquamation and erosion of the skin extended to involve all the treated surfaces. On July 14 obstipation replaced the diarrhea; the vomiting and abdominal pain increased. Drenching sweats, dehydration, pallor and apprehensiveness became prominent. This grave constitutional reaction progressed rapidly. The temperature rose to 105°F., the pulse rate to 130, and the respirations to 33. As abdominal distention and diffuse tenderness increased, the intestinal sounds became inaudible. Except for albuminuria and acetonuria, laboratory tests were negative. Roentgenograms in the erect and prone positions revealed a moderate degree of intestinal gaseous distention, with a number of fluid levels suggesting partial ileus. The diagnosis of radiation necrosis of the bowel with peritonitis was entertained, and conservative measures were instituted. The response to blood transfusions, intravenous injection of fluids, penicillin, streptomycin and Wangensteen decompression was slow, but at the end of 1 week intestinal function appeared to have been satisfactorily restored. The involved skin surfaces displayed promising granulations. On August 5 a barium study exhibited normal esophageal and gastric outlines. The size, contour and peristalsis of the stomach were essentially normal; no filling defects or other pathologic alterations could be demonstrated. The contour of the duodenal bulb appeared smooth, its filling and emptying processes were unhindered, and pressure disclosed a normal mucosal pattern. On films taken at intervals of 1, 3 and 6 hours, slight dilatation of the distal jejunum and irregular barium distribution in the ileum could be identified. Gastric emptying was complete at the end of 6 hours, and the head of the meal was found in the hepatic flexure. After 24 hours the barium was distributed irregularly in the colon. Although the abnormal pattern of the distal jejunum and ileum was considered consistent with changes induced by radiation therapy, demonstrable organic defects were not visualized in the stomach or duodenum.

Except for occasional periods of mild pain in the right upper quadrant, easily relieved by the ingestion of an antispasmodic mixture, the patient remained asymptomatic for 9 weeks after the last x-ray treatment. On September 13 he was suddenly stricken with severe upper abdominal pain, which radiated to the right costal margin and shoulder. Boardlike abdominal rigidity, exquisite tenderness and release tenderness were notable; percussion could not be tolerated.

Examination of the blood showed a white-cell count of 12,850, with 78 per cent segmented granulocytes, 6 per cent stab cells, 13 per cent lymphocytes and 3 per cent monocytes;

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the hemoglobin determination was 13 gm. per 100 cc. Urinalysis was normal. X-ray films of the abdomen indicated the presence of a massive amount of free air beneath the right and left leaves of the diaphragm, signifying rupture of a hollow viscus. Laparotomy was immediately performed. A hiss of escaping gas could be distinctly heard as the peritoneum was incised. There was gross contamination of the peritoneal cavity by the gastric contents, which had emerged through a perforation of the anterior surface of the stomach near the greater curvature about 3 cm. proximal to the pylorus. The opening, about 2 cm. in diameter, was not invested by thickened, edematous or discolored tissue. The edges of the hiatus were approximated without any difficulty. Considerable fibrinous exudate covered the peritoneal surfaces of the intestine, but careful inspection of duodenum and jejunum failed to reveal any signs of radiation fibrosis. There were no recognizable effects of any previous intestinal perforation.

After 5 days of an undisturbed postoperative course, pain and tenderness in the left upper abdominal region and pain in the left shoulder developed. These events were accompanied by a spiking temperature, profuse sweats, leukocytosis, left pleural effusion and a fixed and elevated left leaf of the diaphragm. Conservative treatment of this subphrenic abscess with blood transfusions, measured intravenous injection of fluids, electrolytes and antibiotics effected a gradual termination of all the inflammatory phenomena. Since discharge from the hospital, convalescence has been interrupted by short, afebrile episodes of upper abdominal pain.

A gastrointestinal barium series performed on November 11 failed to reveal any sign of an ulcer or previous perforation. The rugae appeared normal, peristalsis was active, and emptying proceeded at a normal rate. The contour and mucosal pattern of the duodenum appeared entirely normal. At the end of a 2-hour interval, the meal was found in the coils of the small intestine, which were of rather large caliber. The mucosal outline of the small intestine did not present any remarkable abnormalities. Twenty-four hours later the barium was distributed irregularly throughout the colon.

Discussion

The sequence of events suggests that the perforation was attributable to the deleterious effects of high-dosage radiation. The gastric tissues were subjected to 5250r during an interval of thirty-eight days. It is not remarkable that perforation was delayed, for cytolysis and disorganization of the gastrointestinal mucosa have been observed for weeks and months after termination of x-ray therapy.[4] However, the operative disclosure of such a rapidly progressing gastric lesion contrasted sharply with the freedom from radiation effects in the adjacent structures. The stomach permitted unrestricted manipulation for obliteration of the hiatus and did not appear indurated, edematous, discolored or fibrotic. The duodenum and jejunum did not display any noticeable thickening or white fibrosis. Nowhere was tumor infiltration of the enteric tract found. It is equally significant that evidence of a previous perforation was not seen. Apparently, the alarming incident of ileus, toxemia and prostration that immediately succeeded irradiation could not be ascribed to a perforation of any alimentary segment. This early reaction was far more severe than the diarrhea or radiation sickness that ordinarily attends therapy. The morphologic changes held accountable for this syndrome comprise damage and dissolution of the intestinal mucosa. Since the healing residua of such lesions may consist of simple mucosal atrophy rather than recognizable cicatrization, stenosis or fistula,[4] the episode lends support to the thesis of Warren and Whipple[5] that peritonitis can occur without perforation when radiation injury is severe enough to effect an increased permeability of the intestines to bacteria.

This case is similar to those reported from the Walter Reed Hospital,[2, 3] where radiation-induced ulcers developed in 35 out of 256 patients treated for testicular neoplasms. In only 6, however, did complications (hemorrhage and perforation) prompt surgical intervention. Here, as in the case reported above, massive radiation was directed to the lumbar and periaortic lymph nodes and included the stomach within the path of the beams. Every one of the ulcer victims had received more than 5000r to the epigastric area. The fact that other patients have been subjected to similar or greater amounts of radiation without serious consequences indicates that dosage is not the only significant factor. Smaller doses may likewise lead to troublesome complications. The individual idiosyncrasy may be so striking that grave consequences appear after doses that are far below the usual tolerance of the intestinal mucosa. Cathie[6] reported 2 fatal cases of ulceration of the small intestine in which less than 3000r were delivered to the pelvis in the treatment of cervical carcinoma. Brick[7] described a case of an ulcer of the greater curvature incident to 2424r of abdominal radiation. Palmer and Templeton,[8] employing 1100 to 3600r through portals aimed at the upper part of the stomach for the suppression of gastric secretion, encountered a case of harassing diarrhea that developed about three months after therapy. It appears that the vulnerability of the enteric tissues to radiation may be unique and unpredictable.

In direct contrast to these serious necrotizing and ulcerating effects, x-ray therapy has been successfully employed in the treatment of peptic ulcer. Palmer and his associates[8, 9] have demonstrated that histamine-resistant achlorhydria could be induced by irradiation of the fundus and corpus of the stomach. The degree and the duration of secretory depression were variable but when complete elimination of gastric acidity was achieved for a period of ninety days or longer, relief of symptoms and progressive healing of the gastric or duodenal ulcer followed almost invariably; during this period of achlorhydria the ulcer did not recur. The total amount of radiation delivered, however, was much less than that usually given in the treatment of malignant lesions; gastric acidity could be entirely suppressed or profoundly reduced with total-depth doses of less than 2000r. The beneficial effects of radiation-induced achlorhydria upon the course of peptic ulcer appear convincing and add to the significance of the acid factor in the pathogenesis of the disease.

In general, a moderate amount of irradiation appears to inhibit the secretory action of the gastric cells, whereas more intensive treatment may produce severe damage. Tissue destruction, however, is not solely dependent upon the magnitude of radiation. The potential hazards of x-ray therapy cannot be entirely removed because individual sensitivity cannot be detected prior to exposure. Grave complications may be preceded by an unpredictable period of well-being.

Summary

A case of severe reaction to intensive radiation of the epigastrium followed by the development and perforation of a gastric ulcer is presented. Despite the gravity of the gastrointestinal manifestations that immediately succeeded the treatments, x-ray studies did not reveal any ulceration of the stomach or duodenum. Yet two months later an acute perforation of the stomach developed. The possibility of gastric ulceration and perforation after intensive radiation of the epigastrium is to be considered as one of the hazards of treatment.

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MEDICAL PROGRESS

RECENT ADVANCES IN THE ROENTGENOGRAPHIC DIAGNOSIS OF CONGENITAL MALFORMATION OF THE HEART AND GREAT VESSELS

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THE roentgenographic features of certain congenital malformations of the heart and great vessels have recently been clarified. An accurate diagnosis of the nature of the malformation cannot be made without a clear understanding of the basic physiologic changes caused by such a malformation, and only rarely can an accurate diagnosis be made by simple roentgenographic methods alone. The diagnosis should, whenever possible, be based on the history, physical findings, electrocardiogram, film and fluoroscopic examination, and on the simpler laboratory procedures. In some cases it may be necessary to call upon the more complicated ancillary methods of diagnosis, such as angiocardiography, cardiac catheterization and catheterization of the great vessels. In this paper only the more recently recognized roentgenographic criteria for diagnosis will be discussed, with particular emphasis on malformations that are at present amenable to surgery.

Patent Ductus Arteriosus

No specific roentgenographic findings may be observed in patients with a well defined patent ductus arteriosus, and it is probable that a diagnosis by this means cannot be made in the absence of a typical murmur. When characteristic changes are present the heart appears to be slightly enlarged, with hypertrophy of the left ventricle and often slight fullness of the left auricle, which produces slight posterior displacement of the barium-filled esophagus in the right anterior oblique projection. The shadow of the pulmonary artery is usually increased in size, as are the intrapulmonary vessels, which present a normal pattern. The aorta shows no abnormality of size or contour. Perhaps the most characteristic change is an increase in the amplitude of pulsation of the left ventricle, aorta and pulmonary artery, an apparent reflection of the wide pulse pressure and excessive blood reaching the pulmonary artery from the left-to-right shunt. Expansile pulsation of the intrapulmonary vessels, once thought to be frequent, is actually rarely apparent. After ligation or section of the patent ductus there is usually little change in the general size or contour of the cardiac silhouette, but a prompt diminution in the amplitude of pulsation of the left border of the heart may be observed, and the intrapulmonary vessels rapidly become smaller. Aneurysms of the patent ductus have been reported, although most cases have been recognized post mortem in infants. Kneidel[1] believes that it

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should be possible to recognize this anomaly by observation of a smooth, rounded pulsating shadow in the left hilar region in the position of the ductus. The trachea is frequently displaced forward and to the right, and the aneurysm may show a thin shell of calcium deposit in the wall. Calcification in the closed ductus has been observed.[2]

A fenestration in the pulmonary-aortic septum will produce changes indistinguishable from those seen with a patent ductus, as may a high defect of the interventricular septum.

Coarctation of the Aorta

The major roentgenographic features of this anomaly have long been recognized, but in the young child it is to be remembered that no definite x-ray findings may be present. It is usually possible to recognize hypertrophy of the left ventricle, and although rib notching may be seen at a very early age, it is not a frequent finding until after the first decade of life. It is now known that notching of the inferior aspect of the posterior thirds of the ribs is not a pathognomonic sign, since it has been reported in association with collateral vessels[3] in cyanotic heart disease, and one may observe notching due to increased venous pressure, particularly with marked elevation of pressure in the presence of mediastinal venous obstruction. The appearance may be simulated by erosion of the ribs produced by neurofibromatosis of the intercostal nerves. Unilateral rib notching may be of significance. If it is seen on the right alone it usually indicates that the coarctation is proximal to the point of origin of the left subclavian artery, or that the left subclavian artery is obliterated.

Of great importance is the information that the roentgenologist can give to the surgeon before correction of the coarctation is attempted. Fleischner[4] has shown that post-stenotic dilatation of the aorta may be recognized by a characteristic shallow impression on the barium-filled esophagus just below the level of the aortic arch, and that the point of coarctation itself may be identified by a small projection of the barium between the impressions produced by the normal aortic arch and by the post-stenotic dilatation. Accurate visualization of the coarctation itself has been obtained by one of three methods.[5, 6] Angiocardiography has been successful in approximately 65 per cent of patients in showing the area of narrowing. A somewhat more satisfactory method is retrograde injection of the carotid artery, which is successful in perhaps 80 per cent. The most valuable method is retrograde catheterization of the brachial artery and direct injection of opaque medium into the aorta under fluoroscopic guidance. By this means accurate delineation of the deformity should be produced in practically all patients. Infants with coarctation may have marked cardiomegaly. Subaortic stenosis produces enlargement of the left ventricle and occasionally dilatation of the ascending aorta.

Anomalies of the Aortic Arch and Derivatives

Edwards[7] has described in considerable detail the anatomic and embryologic features of the many malformations of the aortic arch that can be reasonably expected to occur. Many of these are susceptible to accurate diagnosis by simple fluoroscopic examination, including study of the esophagus with barium and delineation of the trachea with opaque oil. In rare cases it may be necessary to resort to angiocardiography to distinguish between the varieties of constricting vascular ring. Perhaps the commonest anomaly is the aberrant right subclavian artery, which arises as the last vessel on the aortic arch and crosses the midline to its distribution on the right. It usually passes behind the esophagus, but may occasionally pass between the esophagus and the trachea. In either course it produces a characteristic and readily recognizable impression on the barium-filled esophagus. The impression may be at or below the level of the aortic arch. It runs obliquely from left to right upward, and is of the size to be expected of a normal subclavian vessel. There may be some delay in the passage of the barium beyond the point of compression. This anomaly has been observed as an isolated malformation, or in association with other anomalies of the heart and great vessels.[8] Of particular interest is its rather frequent association with patent ductus arteriosus and its association with tracheo-esophageal fistula.

Cases of pressure upon the anterior aspect of the trachea from anomalous vessels have been reported.[9] The usual cause of such pressure is an innominate artery arising somewhat to the left of the midline and closely applied to the anterior aspect of the trachea as it crosses to the right to reach its distribution. This will produce an oblique filling defect on the anterior aspect of the trachea. Moderate compression of the anterior aspect of the trachea has been observed in patients with an anomalous position of the innominate vein, and it may be associated with a bilobate thymus.

For a clear understanding of the anomalies of the aortic arches, one must assume that the normal position of the left aorta is to ascend slightly to the right of the midline, cross anteriorly in front of the trachea and then descend on the left side. The aorta in this normal position produces a shallow indentation of the left side of the esophagus, and a defect seen in the right anterior oblique. It is possible for the descending aorta to cross again to the right side, passing somewhat behind the esophagus and producing displacement and a shallow indentation on the posterior aspect of the esophagus.

The basic anomaly of the right aortic arch is evidently an aorta that ascends and descends on the right of the esophagus. This produces an extrin-

sic defect on the right side of the esophagus, and a defect seen in the left anterior oblique projection. In this basic deformity no defect on the posterior aspect of the esophagus is seen, and the vessels passing from the aortic arch to their distribution on the left side pass anteriorly to the trachea. Many variations of this anomaly can be recognized with accuracy. The aortic arch may swing behind the esophagus and descend on the left side of the spine, producing a large, rounded filling defect on the posterior aspect of the esophagus at the level of the aortic arch. However, a similar posterior defect may be produced by an aortic diverticulum and may be closely simulated by the left subclavian artery passing from the right aortic arch behind the esophagus to its distribution on the left side.

According to Edwards[7] the ductus arteriosus should lie on the same side as the upper portion of the descending thoracic aorta. It is possible, however, for anomalies to occur when the ductus is on the opposite side. The most frequent of these is a right aortic arch descending on the right of the spine associated with a left ligamentum arteriosum producing a constricting ring.[10] The roentgenographic changes are not difficult to recognize. The aortic mass can be seen on the right side descending on the right and producing the characteristic defect on the esophagus just described. In addition, a small defect on the left side of the esophagus is caused by the left ligamentum arteriosum and a small or shallow impression on the posterior aspect of the trachea as the ligamentum arteriosum passes behind the esophagus to join with the upper portion of the descending thoracic aorta on the right. One may also find a subclavian vessel passing behind the esophagus, and in such cases a double posterior defect is produced, one running obliquely upward from right to left. In these patients the trachea will show some compression, particularly on the right side.

Many varieties of the double aortic arch are found. Without angiocardiographic examination it is often not possible to diagnose every variation, but the basic anomaly can be identified. In most patients the right aortic arch is the larger, although occasionally the right aortic arch may be very small and the left aortic arch large. The size of the defect produced will depend upon the size of each of the arches. Typically there is an indentation of both the right and left sides of the barium-filled esophagus, a large defect indenting the esophagus posteriorly and compression of the trachea in all diameters, with forward displacement of the esophagus and the trachea. If the posterior arch is small the posterior esophageal defect is not large and may well be confused with that produced by a ligamentum arteriosum or other vessel passing behind the esophagus. A variation is to be seen when the aortic arch ascends on the left, crosses over to the right in front of the trachea and descends on the right, with an aortic ring due to persistence of both embryologic arches. A double aortic arch with ablation of one portion, which may then be represented by a simple fibrous band, is also possible. This has been most frequently seen in the right aortic arch descending on the right associated with a left ligamentum arteriosum and a fibrous band as a remnant of the left aortic arch. Roentgenographically, it is probably not possible to distinguish this particular lesion. The position of the vessels arising from the aortic arches may vary considerably and are usually, in view of the nature of the greater malformation, of little significance.

Classification

Several attempts have been made in recent years to establish a simple classification that will prove useful in differential diagnosis when the major malformation lies within the cardiac silhouette. As yet no completely satisfactory diagnostic classification has been presented. Perhaps the best is that used by Peck and Wilson,[11] who divide malformations into cardiac malformations in which cyanosis is present, and those in which cyanosis is absent; since, in nearly all forms of congenital malformation, the pulmonary-artery segment of the cardiac silhouette is altered, they further subdivide patients into those who show an absent and those with a normal or full pulmonary-artery segment. In addition, one must make an effort to classify the type and extent of pulmonary blood flow by observation of the pulmonary vascular markings: whether this is increased or diminished and whether the pattern is that of normal supply from the pulmonary artery, or whether it is the pattern of a compensatory blood flow through the lungs from the bronchial arteries. However, one must remember that it is not possible from roentgenographic examination alone to distinguish between a pulmonary artery enlarged from excessive flow and a pulmonary artery enlarged from increased pressure within the pulmonary vessels.[12]

Malformations with Diminished Pulmonary Blood Flow

Tetralogy of Fallot

In most patients with this malformation a rather characteristic x-ray film is produced.[13] The heart tends to be small with hypertrophy of the right ventricle. The apex is elevated, and the left ventricular border displaced posteriorly. In the anteroposterior and right anterior oblique projections the pulmonary-artery shadow is diminished in size, or may be wholly absent, and there is diminution in the size of the intrapulmonary vessels. At least 20 per cent of these patients show an aortic arch on the right side. This may be associated with any of the anomalies previously described. Occasionally, an abnormal peripheral vascular pattern is seen in the lungs, suggesting that there is a compensatory flow through the bronchial vessels. Angiocardiography will show the overriding of the aorta, as

well as the degree of pulmonary stenosis or hypoplasia. However, the procedure is rarely warranted, since angiocardiography in the cyanotic child or in one with little cardiac reserve is definitely hazardous and carries with it a mortality of perhaps 1 per cent. Occasionally, there may be real indication for the procedure if one cannot recognize pulmonary vessels of sufficiently large caliber to anastomose with the subclavian artery or with the aorta. After successful operation there is usually an increase in the size of the heart, with alteration in the contour due to enlargement of the left ventricle and increase in the prominence of the pulmonary markings. This may be unilateral, depending on the side of shunt.[14]

In the differential diagnosis of the tetralogy the various forms of truncus arteriosus and transposition occasionally give considerable difficulty. The prominence of the pulmonary vascular markings even in early life in the majority of these malformations is an extremely helpful differential point.

Tricuspid Atresia

One may assume that a cyanotic patient who exhibits left-axis deviation and hypertrophy of the left ventricle by electrocardiogram has an underdeveloped right ventricle with either tricuspid atresia or severe stenosis. The x-ray appearance is diagnostic in most cases. The appearance of the heart is evidently dependent upon the size of the interauricular septal defect that, of necessity, accompanies tricuspid atresia if the condition is to be compatible with life. In all cases the left ventricle is enlarged, and there is usually concavity or lack of fullness in the region of the pulmonary artery. The size of the auricles is dependent upon the size of the septal defect. If the defect is large there is no gross auricular enlargement, although slight enlargement of the left auricle may be seen, and there may be actual concavity of the right border of the heart as seen in the anteroposterior and in the left anterior oblique projection. If the interauricular septal defect is small the appearance of the heart may be bizarre, with marked enlargement of the right auricle, which bulges prominently to the right, giving an appearance very suggestive of dextrocardia. The aorta is often somewhat enlarged, and I have observed 5 patients with a right aortic arch. The vascular pattern in the lungs in all cases is abnormal. The normal pulmonary vascular pattern may be markedly diminished, although some blood may reach the pulmonary vessels either by way of a patent ductus or by a diminutive right ventricular outflow tract with an interventricular septal defect. However, in most cases the major peripheral vascular supply to the lungs is by way of the bronchial arteries, and this produces a characteristic fine, mottled and reticulated pattern throughout each lung. Many of these patients do extraordinarily well immediately after an operation to increase the pulmonary blood flow, but within six months a considerable number show rapid increase in the size of the heart, followed by decompensation.

Isolated Pulmonary Stenosis

At least five different forms of pure pulmonary stenosis may occur.[15] Roentgenographically, they may be divided into two groups. All patients show hypertrophy of the right ventricle. The left ventricle may be displaced upward and posteriorly by the enlargement of the right ventricle. If the pulmonary stenosis is of the simple valvular or of the diaphragmatic type there is usually post-stenotic dilatation of the pulmonary artery, producing considerable fullness of the left waist of the heart in the anteroposterior projection, and a prominent pulmonary-artery segment as seen in the left anterior oblique projection. As a rule the other types of pulmonary stenosis, conus separate chamber, subpulmonic stenosis and pulmonary hypoplasia do not show post-stenotic dilatation, and in these patients there is absence of fullness in the region of the pulmonary artery. Amplitude of pulsation of the artery is usually diminished. In nearly all cases it is possible to recognize that although the pulmonary vascular pattern throughout the lungs is not unusual in general appearance, the pulmonary vessels are considerably diminished in caliber, giving the lungs an unusually clear appearance.

If an interauricular septal defect is associated with pure pulmonic stenosis the patients are apt to be cyanotic, with a reversal of blood flow from the right auricle through the septal defect into the left auricle. This usually does not produce as striking a change in the appearance of the cardiac silhouette, but may produce slight enlargement of the left auricle demonstrated by minimal posterior displacement of the barium-filled esophagus in the right anterior oblique projection.

Malformations with Prominent Pulmonary Vessels

A number of congenital malformations of the heart regularly produce increase in the size of the pulmonary artery and marked engorgement of the intrapulmonary vessels. By roentgenographic methods alone it is often difficult or impossible to distinguish between the more important members of this group, but if the x-ray findings are correlated with the clinical and electrocardiographic findings a diagnosis on a broad physiologic basis is usually possible.

An *interauricular septal defect*, if small, produces very little roentgenographic change. If it is large, during the neonatal period and early childhood the heart is frequently considerably enlarged. There is enlargement of the right ventricle and auricle, so that the heart tends to be rather globular in contour. If the shunt is sufficiently marked, even early in life, there will be dilatation of the pulmonary artery and marked increase in the size of the intrapulmonary vessels, and a definite increase in the amplitude of pulsation of both the pulmonary artery and the pulmonary vessels can be seen. In older patients auricular enlargement is usually not evident, but enlargement of the pulmonary artery becomes more marked. The *syndrome of Lutembacher* produces an identical roentgenographic appearance, so that the diagnosis must be based on the previous findings in a patient who exhibits the rumbling diastolic murmur of mitral stenosis.[16] Most patients with an *interventricular septal defect* show no change in the film or fluoroscopic appearance of the heart. However, if the septal defect is high in position the physiologic change is very similar to that produced in the *Eisenmenger complex*, blood being pumped directly from the left ventricle into the pulmonary artery. In these patients the heart is frequently somewhat enlarged, and hypertrophy of both right and left ventricles can often be identified, although this is admittedly difficult to recognize and reliance must be placed upon the electrocardiographic findings to determine ventricular preponderance. The pulmonary artery is prominent, as are the pulmonary vessels, and expansile pulsation can be detected. This lesion may be associated with aortic regurgitation, and if this is present further enlargement of the left ventricle occurs, with a collapsing type of pulsation of the aorta. The Eisenmenger complex produces changes in the heart that are similar, although at times the pulmonary artery shows almost aneurysmal dilatation, and at times the right side of the heart shows the dominant enlargement, perhaps a reflection of the degree of aortic overriding.

Of considerable interest is the recently described entity, the *Taussig-Bing anomaly*,[17] in which the aorta arises from the right ventricle and there is overriding of the pulmonary artery with an interventricular septal defect. These patients are cyanotic from birth, but the roentgenographic appearance is probably identical to that of the other anomalies in this group or to be distinguished only with great difficulty.

Angiocardiography

This procedure has now been used in many thousands of patients and frequently yields valuable diagnostic information not obtainable by other methods. It should be used with caution in cyanotic patients and in patients with a very low cardiac reserve.

The many excellent articles and reviews on the subject indicate the worth of the method.[18-20] It has contributed tremendously to knowledge of the roentgenographic appearance of congenital malformations of the heart and great vessels and will in many cases continue to do so. One should undoubtedly strive for simplification in methods of diagnosis, and it is probable that angiocardiography yields additional information of value in less than 10 per cent of patients with congenital cardiac malformation. The angiocardiographic changes seen in most forms of congenital heart disease have been thoroughly reviewed by Sussman and Grishman,[21] and the reader is referred to this excellent article for further information.

There have been many technical advances in angiocardiography.[22, 23] The most important is the introduction of automatized serial exposures using a roll film, so that multiple serial exposures may be taken at the rate of two to four per second, each roentgenogram being approximately 9½ x 9½ inches. Cinematographic methods of study have been carried out with brilliant results at the University of Rochester School of Medicine and Dentistry.

Cardiac Mensuration

Efforts are still being made to obtain a satisfactory method to determine cardiac size in children

between the ages of three and sixteen years. Maresh[24] has further developed the study of the cardiothoracic ratio, and Meyer[25] has devised a nomogram that gives a direct reading of the percentage variation from the expected normal. As yet, the practical diagnostic value of cardiac measurement in young children is not evident, since cardiac enlargement is not found in many of the very severe malformations.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 36191

PRESENTATION OF CASE

An eight-year-old boy entered the hospital because of aching pain in the right knee and thigh of five weeks' duration. He described the pain as being to the right of his kneecap, radiating laterally and distally and a similar ache in the mid-thigh anteriorly, which radiated up and down. The pain was not constant, was more frequently felt at night or at rest and was not aggravated by walking or running. It was unrelated to any known trauma although he was a very active youngster and not prone to notice minor bumps and bruises. There had been little change in the character of the pain although it had possibly become a little more severe. A feeling of restlessness in the right leg caused the patient to move it frequently.

Physical examination showed an alert, active, healthy-looking boy. The examination was entirely negative except for tenderness to deep pressure along the medial aspect of the entire proximal portion of the right tibia and slightly increased local heat. The legs were of equal length, and the calves of equal circumference. The right proximal thigh was 1 to 2 cm. larger in diameter than the left. The right hip lacked 10° of full flexion, with discomfort in extreme flexion. Internal rotation, external rotation, abduction and adduction were essentially normal.

The temperature was 99°F., the pulse 100, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The urine was normal. The hemoglobin was 13.8 gm. per 100 cc. The white-cell count was 8700, with 57 per cent neutrophils, 30 per cent lymphocytes, 10 per cent monocytes, 1 per cent eosinophils and 2 per cent atypical lymphocytes. The calcium was 9.8 mg., the phosphorus 3.6 mg. and the alkaline phosphatase 7.0 units per 100 cc. X-ray films of the chest were normal. X-ray study of the right femur demonstrated fairly symmetrical new-bone

formation involving the upper shaft of the femur over a distance of about 7 cm. (Fig. 1). The cancellous portion of the shaft opposite the periosteal change showed an area of increased density, apparently with pressure erosion or actual destruction of the inner aspect of the cortex laterally.

On the third hospital day an operation was done.

Differential Diagnosis

Dr. Thomas J. Anglem*: This is a brief and reasonably straightforward history compatible with any number of different lesions that may occur in the long bones. The triad of pain, swelling and dysfunction that this patient presented is seen with a great variety of lesions. One feature of this history is the lack of any definite diagnostic criteria, although there are several points that may be helpful in arriving at a diagnosis. One is the complete absence of any evidence of systemic disease. The patient apparently was in good general health, and had a normal blood count, normal blood chemical findings and a rather mild degree of subjective symptoms. A puzzling point in the history is the reference to tenderness and local heat in the region of the proximal tibia. In the absence of any x-ray report of the tibia, I have to assume that if an x-ray examination was made it was negative. Frequently, pain in the tibia may be referred from a lesion in the femur, but in my experience I have not observed local heat or tenderness this distant from a known lesion.

At this point we might look at the x-ray films. I think the diagnosis must rest almost wholly on the interpretation of the films.

Dr. Stanley M. Wyman: The lesion is well seen, extending from a point below the lesser trochanter down the shaft of the femur, and is characterized chiefly by periosteal new-bone formation, with a suggestion of layering. There is a large central area of rarefaction in the bone that comprises perhaps two thirds of the length of the entire lesion. I think this area of rarefaction is extremely large for osteoid osteoma, and for the usual types of infectious processes, such as low-grade osteomyelitis. I do not think I have seen it with Ewing's sarcoma. The other examinations were negative.

Dr. Anglem: My opinion about osteoid osteomas was the same. I thought that the area was too large and that it was unlikely that this was a bone abscess. The absence of any antecedent history, the normal white-cell count, the virtually normal temperature and the slight degree of new-bone formation make me quite certain that it was not a chronic or low-grade bone abscess.

Of the various possibilities, it seems to me that four have to be considered seriously. The first is a rather uncommon condition, eosinophilic granuloma. The patient was in the right age group for this lesion, which occurs predominantly in children and adolescents and produces a destructive lesion, usually without new-bone formation. Although the condition occurs more often in flat bones, it also involves the shaft of long bones and produces a fairly sharply defined area of radiolucence, which I think in most cases has a more punched out appearance than this particular lesion had. Eosinophilic granuloma is of unknown etiology, and in 20 to 50 per cent of cases it is multiple. I suppose the tenderness in the tibia may be explained on the basis of a second lesion in that region. It is not common to find periosteal new-bone formation associated with this lesion although it can occur when there is perforation of the cortex, but this does not appear to have been present in this case. I think the lesion was probably not eosinophilic granuloma, which must be considered, however.

Figure 1.

*Visiting surgeon, Massachusetts Memorial Hospitals; assistant professor of surgery, Boston University School of Medicine.

The second lesion that I think must be considered, despite the fact that this was not a typical clinical picture, is Ewing's sarcoma. Ewing's sarcoma is probably the most common primary malignant lesion of bone at the age of eight. This tumor, which occurs most frequently in childhood and adolescence, has a predilection for the male sex. When Ewing's sarcoma involves the long bones, it has a definite preference for the midportions of the bones — the diaphyseal region of the shaft. It is a purely destructive lesion without formation of tumor bone and characteristically produces periosteal new-bone formation, which is usually laid down in layers, forming the so-called onion-skin appearance that was apparent in the case under discussion but not markedly so. However, Ewing's sarcoma characteristically produces some degree of systemic reaction in most cases, usually more than was apparent in this particular case. The patients are sicker than this boy appeared to be, and are likely to run a higher temperature — often up to 102 and 103°F. — and to have anemia and leukocytosis. In the typical Ewing's sarcoma the destroyed area in the cancellous portion of the bone usually presents a much more irregular, moth-eaten, honeycombed appearance than was observed here.

Osteogenic sarcoma cannot be dismissed entirely. In children osteogenic carcinoma usually presents an atypical picture and not uncommonly occurs in the diaphyseal portions of the shaft whereas ordinarily it is most commonly seen in the metaphysis. Osteogenic sarcoma at this age can produce a picture that is indistinguishable roentgenologically from Ewing's sarcoma and has to be considered also.

The lesion, however, that seems to me to fit the picture in this case most accurately is central chondrosarcoma. This tumor begins centrally, characteristically produces some erosion of the adjacent cortex and, when it occurs in the thicker portion of the shaft as the lesion did here, characteristically produces some degree of new-bone formation. The radiologic picture is an oblong translucent area of destruction in the shaft of the bone surrounded by a dense shell made up of periosteal new-bone formation. Considering all the factors, including the absence of any evidence of a constitutional disturbance, I think the diagnosis of central chondrosarcoma fits the picture most accurately, and it is the diagnosis that I shall make.

Dr. Grantley W. Taylor: I might risk a diagnosis on x-ray findings up to a point but I should think the diagnosis of bone tumor should rest on the microscopical result in the last analysis. I wonder why Dr. Anglem did not consider reticulum-cell sarcoma.

Dr. Anglem: For one thing I do not believe there has been any case in a patient as young as this reported.

Dr. Taylor: I have seen some cases.

Dr. Anglem: The x-ray picture of reticulum-cell sarcoma shows a more irregular destructive and mottled appearance than that in this case.

Dr. Milford D. Schulz: Chondrosarcomas, however, usually arise from places where cartilage once was deposited.

Dr. Anglem: They can occur in the shaft of the bone.

Dr. Wyman: The correct diagnosis was made by one of the members of the X-Ray Department but not by me, unfortunately. I considered a low-grade inflammatory process or Ewing's tumor. I do not think we were as much concerned by chondrosarcoma, however.

Dr. Eugene E. Record: It was our impression that it was Ewing's tumor or low-grade infection. At operation, performed by Dr. Joseph S. Barr, the incision was made on the posterolateral aspect of the right thigh. The periosteum was incised and came away freely from the bone as it does in a child of that age. The surface of the bone was roughened and obviously thickened, and a block of bone about 5 cm. long and 1 cm. wide was removed. From the marrow cavity of the bone, gray, granulomatous material was curetted. We thought it was probably a low-grade osteomyelitis.

Clinical Diagnosis

? Ewing's tumor.
? Osteomyelitis.

Dr. Anglem's Diagnosis

Central chondrosarcoma.

Anatomical Diagnosis

Eosinophilic granuloma of bone (femur).

Pathological Discussion

Dr. Benjamin Castleman: I was at the operation and did a frozen section of the material, which showed a number of inflammatory cells. I believed that they were mostly polymorphonuclear leukocytes, so that I reported it as probably an osteomyelitis. The one thing we wanted to rule out was Ewing's tumor or any other neoplasm. Our final sections showed that there were polymorphonuclear leukocytes, but they were all eosinophilic, and in addition between the islands of eosinophils were large histiocytes, which are quite characteristic of eosinophilic granuloma. Cultures and smears of the material were negative.

It was believed that the patient should not receive x-ray treatment because the granuloma was too near an epiphysis, and he was sent home.

Dr. Taylor: Do we have a follow-up report?

Dr. Castleman: So far the child has been well. It was only about five or six weeks ago that he was operated upon. X-ray films of the other bones are all normal.

DR. ALLAN M. BUTLER: What was it about the x-ray appearance that enabled somebody in the X-Ray Department to make a definite diagnosis?

DR. WYMAN: Dr. William R. Eyler made the correct diagnosis on the basis of the large area of rarefication and the extensive periosteal new-bone formation, which has been recently described as going with a few of these eosinophilic granulomas.*

*Hansen, P. B. Relationship of Hand–Schüller–Christian's disease, Letterer–Siwe's disease and eosinophilic granulomas of bone. *Acta radiol.* 32:89-112, 1949.

CASE 36192

PRESENTATION OF CASE

A nine-year-old boy entered the hospital because of pain in the upper lumbar region of the back.

The patient apparently developed normally and was healthy until three or four months prior to admission, when he first complained of discomfort in the back when bending over to tie his shoes or pick up objects from the floor. When he made such movements he was observed to keep his lumbar spine stiff. When the back pain persisted and led to more marked restriction of the lower spinal movements, the patient was taken to the Orthopedic Department Clinic. There, x-ray examination of the lumbar spine revealed a large defect with smooth margins involving the lamina of the second lumbar vertebra and an inferior articular process of the first lumbar vertebra (Fig. 1 and 2). There was no soft-tissue mass, and the lesion was symmetrical in its involvement.

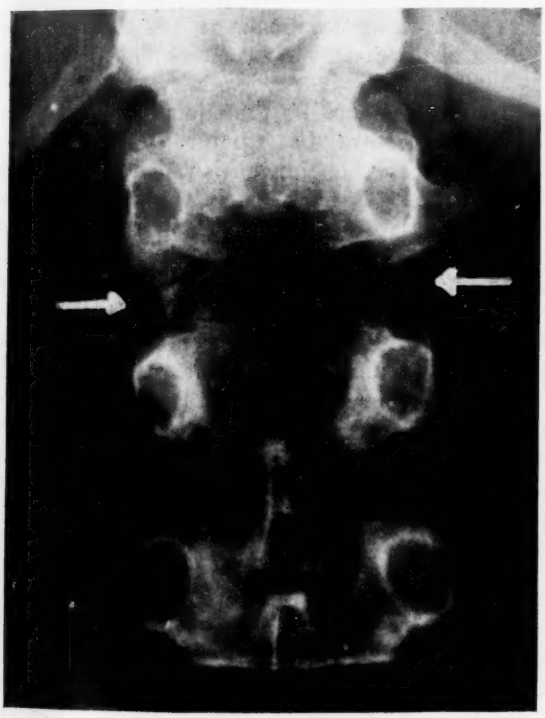

FIGURE 1. *X-Ray Film of the Lumbar Spine. Arrows point to expanded, destroyed lamina of first lumbar vertebra.*

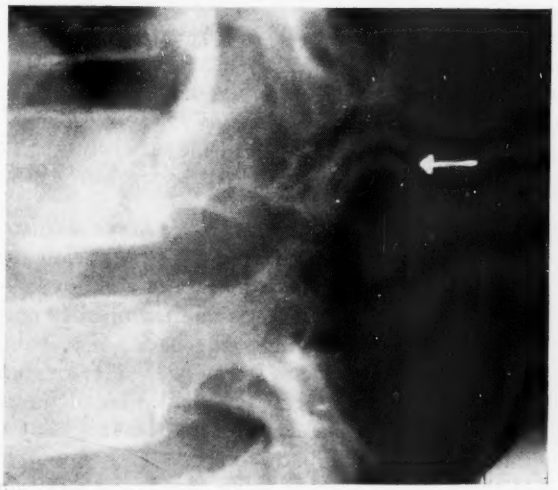

FIGURE 2. *X-Ray Film of the Lumbar Spine. Arrow points to expanded, destroyed lamina of first lumbar vertebra.*

The patient was admitted to the hospital, where physical examination revealed a well developed and well nourished boy. There was loss of the normal lumbar lordosis, and that portion of the spine was held rigidly with a moderate degree of spasm of the sacrospinalis muscles. Forward flexion was limited to 50°, and hyperextension to 15°. Lateral flexion was not limited. A tender mass was palpable overlying the first lumbar vertebra, whose spinous process could not be made out although that of the first and third did not seem unusual. Straight-leg raising was accomplished to 80° bilaterally without difficulty. No muscle atrophy or weakness was demonstrable. There was no evidence of spinal-cord or nerve-root involvement. There were no sensory changes, and the deep tendon reflexes were bilaterally equal and active.

Examination of the blood showed a white-cell count of 6400, with 60 per cent neutrophils, 30 per cent lymphocytes, 9 per cent monocytes and 1 per cent eosinophils. The blood smear was not unusual. The hemoglobin was 12.8 gm. The urine was normal. The sedimentation rate was 20 mm. per hour (Westergren method). Tuberculin tests in 1:100,000 and 1:10,000 dilutions were negative. The eosinophil count was 106 per cubic millimeter. The blood Hinton

test was negative. The blood calcium was 10 mg., the phosphorus 4.1 mg., and the nonprotein nitrogen 26 mg. per 100 cc., and the phosphatase 5.1 units per 100 cc. Lumbar puncture in the fourth lumbar interspace showed an initial spinal-fluid pressure equivalent to 220 mm. of water with clear fluid, and tests revealed no spinal block. The final pressure was equivalent to 170 mm. of water after removal of 7 cc. of fluid. The spinal-fluid protein was 16 mg., and the sugar 94 mg. per 100 cc., and the Pandy test showed a slight trace of globulin. Further x-ray studies, including a metastatic series, examination of most of the long bones and an intravenous pyelogram, were negative.

On the eighth hospital day an operation was performed.

Differential Diagnosis

Dr. Milford D. Schulz*: We have a history that is remarkable in its paucity of significant complaints. Essentially, it is a history of a nine-year-old boy who was well until three months prior to entry, when he developed pain in the back. The painful back was probably due to spasm of the erector spinae muscles, which produced the limitation of motion. I suppose the spasm was due to the fact that the spinous process was diseased.

I think the important thing here is the x-ray findings; it seems that the entire diagnosis had best rest with them. I disagree with the interpretation as given in the protocol that the process also involved the small parts of the second lumbar segment (Fig. 1 and 2). The process was largely osteolytic and caused expansion of the bone. The spinous process of the first lumbar vertebra was expanded, and the laminas were expanded and pushed out as compared to the normal vertebras. The pedicles were not spread or destroyed. Whether or not the right transverse process was intact or was involved in the process is somewhat equivocal. The lateral view showed a rather widely expanded spinous process of the first lumbar vertebra only. The inferior articular facet seemed to be practically wiped out. There was no sclerosis. There seemed to be a few septums going across the expanded and very much destroyed bone. I cannot say with certainty that there was any breaking through of the cortex, and I could not find any evidence of involvement of the adjacent bone structure.

I suppose I am entitled to the opinion of a radiologist like anybody else.

Dr. Stanley M. Wyman: I went over these films, and I think the lesion was limited to the first lumbar segment without involvement of the adjacent vertebras.

Dr. Schulz: I chose my supporter, you see.

As to what this is, Dr. Brailsford[1] to the contrary, I think I agree with Dr. Channing Simmons and Dr. Grantley W. Taylor that about all the radiologist can tell in a situation like that is that there is something wrong, and that the histologic nature of the process must be determined by the pathologist.

Was this lesion in the bone or outside the bone? If it was outside the bone, what could it have been? Something in the neural canal, probably a tumor arising from the spinal cord or from the meninges, such as a dural cyst or a neurofibroma, I suppose, could give at least the appearance of widening of the laminas, but such lesions should not cause widening of the bone mass as a whole and there should be evidence of the widening of the interpedicular spaces. However, the spaces between the pedicles as a whole are not distorted. Moreover one would expect a tumor arising in or near the spinal cord to cause some signs of cord disturbance, which apparently were not present. Another possibility is a meningocele projecting posteriorly but that should not give rise to increase in the outer dimensions of the bone as a whole. I think we will have to say that this was something inside the bone.

Can it have been a developmental or congenital anomaly? I suppose one might include fibrous dysplasia as developmental, and that can do some very queer things to bone, as can the metabolic diseases of the bone, such as eosinophilic granuloma or Gaucher's disease. As demonstrated by the previous case[2] eosinophilic granuloma can cause not only destruction of the structure of bone but also expansion of the bone, but this usually causes some bone reaction. The process in the case under discussion was largely expansive and osteolytic, and there was no reactive bone. The spleen was not enlarged, and there were no other bones involved so that I think we can dismiss the metabolic diseases.

So far as infection is concerned, of course, everyone thinks of tuberculosis in the spine first of all. I do not recall ever having seen tuberculosis involving the small parts of the vertebra alone. Usually, it involves adjacent segments and the body. On the basis of statistics alone, I should think we might dismiss that as well as the other types of infections. There were no real signs of infection.

This brings us down to some kind of tumor. Metastatic cancer? Usually, cancer metastasizing to bone causes destruction of bone, or if it grows slowly enough sets up reaction in the bone and increases its density, but there are very few that involve the shaft of the bone and expand it; however a few do, carcinoma of the kidney being a typical one. Carcinoma of the kidney in this age group would be unusual, and urograms were normal. The common tumor metastatic to bone in children, of course, is neuroblastoma, which is widespread in its involvement and destructive but does not expand bone.

Osteogenic tumors? The vertebras are queer bones and I suppose an osteogenic sarcoma could give rise to a very queer appearance there. There was no evidence of bone sclerosis and no periosteal reaction.

*Radiologist, Massachusetts General Hospital.

An osteogenic tumor should not just blow bone out as though somebody had been in there blowing soap bubbles. One might say the same thing about Ewing's tumor and reticulum-cell sarcoma.

Lymphoma involving bone surely can do this. Such involvement is unusual at this age, as is myeloma. A tumor located almost exclusively in or about the cord or spinal column is the chordoma, which arises from a rest of the notochord that lies ventral to the cord. Although chordoma may be found rather remotely, I do not believe I have ever heard of one arising in the small parts of the vertebra. To my knowledge, the youngest patient we have seen here with a chordoma was something like eighteen years of age — although chordoma should be a disease of the young. Malignant soft-tissue tumors adjacent to the bone, such as sarcomas and synoviomas, can destroy bone — sometimes very rapidly — but should not expand bone as this did.

The embryologic origin of this part of the body is rather complex, and many parts of endochondral origin come together to form one segment here; I suppose it is quite possible that a little piece of cartilage went wrong, and this lesion might have been the result of that process — an endochondroma or chondrosarcoma or even perhaps one of the tumors that Jaffe and Lichtenstein[3] have described, a benign chondroblastoma. I do not think we have ever heard of a chondroblastoma in the spine, but I think I should mention it.

A simple cyst of the bone should be considered. Cysts are usually in a long bone near the epiphysis, but I do not see how one can eliminate that possibility. Again, I do not know whether they are reported to occur in the spine. Just to give a few more possibilities, I believe one might raise the question of angioma. Angioma usually involves the body of the vertebra but I do not recall ever having seen one in a youngster. Then, of course, there is the endosteal fibroma or neurofibroma.

I believe this was a giant-cell tumor, although I have no right to say so. Giant-cell tumors are not common in children of this age, but they do occur. They expand bone, they can give the appearance of osteolysis of bone that they have expanded, and they leave behind small trabeculae which, I believe, can be seen here. Incidentally, I should like to say in passing that if two adjacent vertebras, with a piece of cartilage in between such as an inferior and superior articular facet of the first lumbar or of the twelfth dorsal vertebra, were involved in the process that would not necessarily mitigate against a giant-cell tumor, which occasionally jumps across a joint space. I think we must say that this was a lesion of the spine that expanded and destroyed the small parts of one segment and that it should have been investigated surgically as it was, and that the exact diagnosis had to be made by the pathologist.

As a rule the length of a radiologist's report is often inversely proportional to the certainty of his diagnosis and the extent of his information — that is an indication of the certainty of the diagnosis here.

Dr. Benjamin Castleman: Will you tell us the operative findings, Dr. Boylston?

Dr. E. F. Boylston: We made an incision over the palpable spinous process and found a reddish-brown mass that was quite lumpy. There was no bone recognized as such. The bone was completely destroyed over the posterior elements. There were several small cortical flecks, but we could not recognize any part of the spine or lamina as such. Destruction apparently went all the way to the epiphyseal joint, which appeared to be intact upon palpation but was not exposed. The mass was scooped out with the index finger. There was no way to tell whether the lesion was destroying from within or from without, the destruction being so total.

Clinical Diagnosis

Tumor of vertebra.

Dr. Schulz's Diagnosis

Giant-cell tumor of first lumbar vertebra.

Anatomical Diagnosis

Fibrous dysplasia of vertebral spinous process.

Pathological Discussion

Dr. Castleman: The material submitted was made up microscopically of long, spindle-shaped cells characteristic of connective tissue, among which were deposits of immature bone and cartilage. These findings are quite consistent with fibrous dysplasia of bone. We have never seen this lesion in this location before, and I have never heard of one breaking through the outer surface of the bone before, but the histology certainly fits it better than any other condition. It is a benign lesion. It had one thing that most of the cases of fibrous dysplasia do not have, and that was a fair number of giant cells but these can easily be accounted for as a reaction to the break in the cortex. The fibrous stroma, the appearance of the cartilage and the immature bone throughout the lesion do not fit in with either a giant-cell tumor or a neurofibroma. I am quite sure that the best diagnosis is fibrous dysplasia. The expansion of the bone is quite characteristic of fibrous dysplasia.

Dr. Schulz: Could you not call it a fibrous variant of a giant-cell tumor?

Dr. Castleman: No.

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THOUGHT CONTROL

PROBABLY the most outstanding, and the most vicious, achievement of twentieth-century dictatorships is the technic known as thought control. By the adroit use of the radio, the press and the open meeting the intellectual development of enormous masses of people can be controlled to an extremely fine point by the state.

Nor is the objective scientist immune from the ceaseless pressure of thought control. The much-publicized controversy between two groups of Russian geneticists abundantly illustrates the low levels to which scientific endeavor may fall when thought control prevails. T. D. Lysenko, apparently an indifferent scientist but a very astute opportunist, evolved a theory of genetics that is in thorough accord with Communist principles. The fact that his theory rests on spurious experimentation made no impression on the Central Committee of the Communist Party, which examined the report and approved it and thereby undermined what support was left for honest, objective scientific research in Russia. At a meeting of the Lenin Academy of Agricultural Sciences,[1] Lysenko crucified his critics and, with the backing of the Central Committee, gained ascendancy over all Russian research activities in the agricultural and related sciences. Several stalwart scientists, whom he singled out for attack, made eloquent defenses of objective research, but to no avail. To medical scientists, the commotion among the Russian geneticists may seem nothing more than a storm in a teacup. There is good evidence, however, that various medical fields are being reoriented in Russia to conform to the views of the new dean of Russian science.[2]

The medical sciences in other countries that have come into the Russian orbit are apparently being actively "purified." Lysenko's coup was made possible by the view that science must be subservient to ill conceived, cynical and unproved political doctrine. In this connection one Hungarian scientific official[3] is quoted as follows:

> . . . Science is the product of social work and will remain a means and a weapon of class warfare as long as rival classes exist. . . . A proletarian partisan outlook insures *de facto* objective knowledge and proletarian partisanship is a *sine qua non* of real science.

This, the classic totalitarian attitude toward science, seems ridiculous to western minds; without thought control it would probably seem ridiculous to Russian minds as well.

Where thought control prevails, the scientific press must participate. The editors of the Roumanian *Revista de Oftalmologie* apparently did not realize this when they permitted the publication of excerpts from the writings of western ophthalmologists. That journal, according to the *New York Times* correspondent in Vienna,[3] was disciplined for its ineptitude, and the full extent of its shortcomings was made clear by one Professor Traian Savulescu. "Numerous Soviet ophthalmologists," said Professor Savulescu, "guided by the scientific conception — the only correct conception — of dialectical materialism, under the direction of the Communist Party of Soviet Russia and with the strong

support of the Soviet Government, have succeeded in raising the ophthalmological science of their country to a level which has made possible the solution of the main problems in this field." The impact of this unhappy episode on the editors of other scientific journals in Roumania is not recorded, but he who failed to see the handwriting on the wall would be obtuse indeed.

In the years that have elapsed since the collapse of the Axis Powers the American medical profession has been able to return to its labors without hindrance. The American doctor, whether practitioner or researcher or both, can publish his opinions with the certain knowledge that at the worst he will suffer no greater indignity than a barbed comment from a dissenting colleague. Repetition of the Russian scientific debacle in this country is virtually impossible, but the American scientist has good reason to look with suspicion on any attempt to compromise his freedom of scientific thought and expression. Military and political expediency are often insufficient explanations for official proscription of certain types of research or of free discussion of scientific topics. From small beginnings ugly edifices may grow.

Thought control is dangerous business.

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2. Brozek, J. Extension of political domination beyond Soviet genetics. *Science* (in press).
3. MacCormac, J. Reading by red star light. *The Saturday Review of Literature*, February 25, 1950. P. 9.

LACK OF EFFECT OF ANTIHISTAMINIC DRUGS ON COMMON COLD

The use of antihistaminic drugs in the treatment and prevention of the common cold has recently received considerable comment and publicity in both the medical and lay press. It has also been trumpeted throughout the nation in newspapers, magazines and radio advertising since the release of the antihistaminic agents for over-the-counter sale by the Food and Drug Administration and the appearance of the now classic article in the *Reader's Digest* upon which most of the lay advertising was based.

The Council on Pharmacy and Chemistry of the American Medical Association made a critical analysis of the data upon which the claims for the value of the antihistaminics in the common cold rested. This report of the Council, which was commented upon recently in these columns, shed some doubt on the validity of the conclusions that were based on these data and also contained recommendation for studies that would supply more reliable and more valid data from which the true value of the antihistaminic drugs in the prevention and treatment of the common cold could be assessed. These recommendations, though sound in principle, did not appear to be very realistic in terms of studies that could reasonably be carried out. It was anticipated, however, that some carefully controlled studies by reliable observers would soon be forthcoming and would either support or refute the rather exorbitant claims that have been made.

A report of one such study appears elsewhere in this issue of the *Journal*. The authors have had extensive experience with acute respiratory diseases and are eminently qualified to undertake and evaluate data in this rather difficult field. The studies included both a "practical usage test" in the naturally occurring disease and a controlled investigation in the experimentally induced disease. Both studies, which gave results that are certainly as valid as any that have thus far been adduced, indicate that the antihistaminic drugs in the usually recommended doses have no beneficial effect whatsoever on naturally occurring common colds or other undifferentiated respiratory diseases. They show further that the drugs neither prevent nor in any way alter the character, course or duration of experimentally induced common colds in human volunteers.

The article in the *Reader's Digest* had the very compelling title "Is This, at Last, Good-Bye to the Common Cold?" One wonders if the author and editor will follow up this article with another giving the answer to this question as based on the reports that are now being made available.

RECOGNITION OF FOREIGN MEDICAL SCHOOLS

The Council on Medical Education and Hospitals of the American Medical Association has been giving serious consideration to the problem of the graduates of foreign medical schools in this country

and has finally published a preliminary list of schools that it has ventured to approve.[1] The list consists of 1 Danish and 2 Finnish schools, 4 in the Netherlands, 1 in Norway, 3 in Sweden, 10 in England, 4 in Scotland and 1 each in Northern Ireland and Wales.

This list has been prepared jointly by the Council on Medical Education and Hospitals and the Executive Council of the Association of American Medical Colleges, which "are of the opinion that medical institutions and medical organizations in the United States would be justified in considering current and past graduates of the . . . foreign medical schools on the same basis that they consider graduates of approved medical schools in the United States."

The vastly increased numbers of graduates of foreign medical schools who have flocked to America in the last decade and a half have given rise to a situation that has never existed before. Many of them have been found so inadequately trained that they could nowhere qualify for registration, and a number of states eventually have debarred them even from taking the examination for registration. Massachusetts in particular does not now admit to examination a physician who matriculated from any foreign school, Canada excepted, later than January 1, 1941.

It is recognized, however, by the Council on Medical Education and Hospitals, that American tradition places on licensing bodies "an obligation not to deny the opportunity to practice his profession to any citizen or prospective citizen who can demonstrate satisfactory qualifications as to his professional competence and character."

In the business of obtaining sufficient information regarding the quality of foreign medical schools and the standards that they have been able to maintain during and since the war, the Council has been diligent. Much of the work, as described in the *Journal of the American Medical Association*,[2] has been done by the Committee on Foreign Medical Credentials, which is an unofficial body sponsored by the Council, and composed of representatives of a number of organizations interested in the problem of foreign physicians. It appears that the investigations have been thorough, even in view of the obvious difficulties that have been encountered, and the recommendations of the Council should, as usual, be trusted.

This country, embarrassingly late, accepted its responsibility in offering a haven to certain of Europe's displaced persons. It must now go the whole way in giving to those who are qualified the opportunity to carry on the work for which they have been trained.

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1. Council on Medical Education and Hospitals. Foreign medical schools. *J. A. M. A.* **142**:587, 1950.
2. Council on Medical Education and Hospitals. Licensure of foreign medical graduates. *J. A. M. A.* **139**:1103, 1949.

COUNCIL OF THE NEW ENGLAND STATE MEDICAL SOCIETIES

New England again gave a demonstration of regional responsibility and solidarity in the meeting on national health legislation held under the auspices of the Council of the New England State Medical Societies at the Copley Plaza Hotel, in Boston, on March 22. This well attended meeting was planned primarily to acquaint officers and interested committees of state and county medical societies and their woman's auxiliaries with current national legislation.

Without attempting here to offer any comments on this legislation, it can simply be stated that each of the six most important major health acts before Congress was briefly analyzed by an informed representative of one of the six state medical societies of New England. After each presentation, Dr. Joseph S. Lawrence, director of the Washington office of the American Medical Association, reviewed the progress of the legislation in Congress.

In this way the merits as well as the defects of the bills on National Compulsory Health Insurance (S. 1679), School Health Services (S. 1411), Federal Aid to Medical Education (S. 1453), National Health Act of 1950 (S. 2940), Social Security Amendments (H. R. 6000) and the National Health Act of 1949 (S. 1970) were presented to an intelligent and thoroughly responsive audience, drawn from all the New England states and keenly aware of the grave hazards to which the country is being subjected.

Dr. Elmer L. Henderson, president-elect of the American Medical Association, gave the evening

address on "The American Medical Association's Position on Pending National Legislation."

It is heartening to witness the increasing respect in which the Council is being held and the quiet leadership that it is offering in matters common to all New England. Its president, Dr. Norman A. Welch, of Boston, and the secretary, Mr. John E. Farrell, of Providence, are to be congratulated on these accomplishments.

At the annual meeting of the Council held in Boston on April 19, the six New England states being represented, the following officers were elected for the coming year: president, Dr. Roland E. McSweeney, of Brattleboro, Vermont; vice-president, Dr. Joseph H. Howard, of Bridgeport, Connecticut; secretary-treasurer, Dr. Creighton Barker, of New Haven, Connecticut. A special tribute was paid to Mr. John E. Farrell, of Providence, who has served as secretary-treasurer during the past five years.

A man was choked to death in England, by swallowing, or rather in attempting to (we were going to say a sheep), a piece of mutton weighing upwards of an ounce and a half, and measuring 2 3/4 inches by 4 inches.

Boston M. & S. J., *May 8, 1850*

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Owing to the number of applications for luncheon for the Section of Ophthalmology and Otolaryngology at noon on Wednesday, May 17, it will be held in the Oval Room of the Hotel Bradford, Boston, instead of at the Hotel Statler as originally announced.

DEATHS

KELLY — John J. Kelly, M.D., of Marlboro, died on December 20. He was in his seventy-ninth year.

Dr. Kelly received his degree from Tufts College Medical School in 1904. He was formerly school physician and a member of the staff of Marlboro Hospital.

His widow survives.

NICHOLS — John H. Nichols, M.D., of Danvers, died recently. He was in his eighty-fourth year.

Dr. Nichols received his degree from Harvard Medical School in 1892. He was formerly superintendent of the Tewksbury State Infirmary and was a member of the American Psychiatric Association.

Two sisters and a brother survive.

BOOK REVIEW

Radiologic Exploration of The Bronchus. By S. DiRienzo, M.D. Translated by Tomas A. Hughes, M.D., and with a foreword by Richard H. Overholt, M.D. 8°, cloth, 332 pp., with 466 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $10.75.

Except as a remarkable collection of expertly reproduced bronchograms, this volume can be recommended only with caution. Granted that the author stresses the valuable concepts of precise description of the bronchial tree and appreciation of its dynamic nature, one is left with the impression that a method has been exploited beyond its clinical limits. This impression may be heightened by a rather awkward translation. Certainly, the material presented is of great interest and is selected from a rich clinical experience. However, the implication of the volume is that bronchography is the *sine qua non* of x-ray diagnosis of pulmonary disease, and argument by specific example or enumeration is brought in support of this thesis. Artifact in this shadowy realm is mentioned but not stressed.

One chapter, indeed, stands out — namely, the one dealing with hydatid disease of the lung. The author discusses at length the radiologic features of this unfamiliar disease and demonstrates clearly its various aspects. The chapters on bronchiectasis and pulmonary suppuration are interesting and well illustrated. So far as cancer of the lung is concerned, one might take issue with the conclusions that bronchography is of greatest use in its diagnosis and should be almost indiscriminately employed. The author's examples of bronchography in asthma and emphysema are interesting in their demonstration of bronchial trees that many would not lightly subject to bronchography, but it is questionable whether the information obtained justified the risk or effort. The opening chapters on embryology, anatomy and physiology of the bronchi are sketchy and suffer in translation.

However, it must be remembered that the author presents a method of bronchography that is not in general use in this country. The method has much to commend it, for by following a radio-opaque oil as it flows into the various segmental bronchi and making spot records of its progress one can certainly learn much. In the author's hands much has been learned, but it is not clear that in many cases equally valuable or even more definitive data might have been gained by simpler means.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Transactions of The Third American Congress on Obstetrics and Gynecology. Municipal Auditorium, St. Louis, Missouri, September 8 to 12, 1947. Edited by Geo. W. Kosmak, M.D., and Robert N. Rutherford, M.D. Portland, Oregon: The Western Journal of Surgery Publishing Company, 1948. $9.00.

Manual of Medical Emergencies. By Stuart C. Cullen, M.D., professor of surgery, and chairman, Division of Anesthesiology, State University of Iowa College of Medicine; and E. G. Gross, M.D., professor of pharmacology and head, Department of Pharmacology, State University of Iowa College of Medicine. 12°, cloth, 267 pp., with 29 illustrations. Chicago: Year Book Publishers, Incorporated, 1949. $3.75.

NOTICES

ANNOUNCEMENT

Dr. Timothy A. Lamphier announces the opening of his offices for the practice of general surgery and proctology at 47 Bay State Road, Boston, and 572 Washington Street (Seiler Building), Wellesley.

HARVARD CHAPTER OF ALPHA KAPPA KAPPA

A meeting of the Harvard chapter of Alpha Kappa Kappa will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, May 16, at 8 p.m. Dr. Cushman D. Haagensen, director of the Institute of Cancer Research and associate professor of clinical surgery, Columbia University College of Physicians and Surgeons, will speak on the subject "Cancer of the Breast — What Hopes Have We for Its Control?" Dr. Ira T. Nathanson will lead the discussion.

MASSACHUSETTS MEDICO-LEGAL SOCIETY

The annual meeting of the Massachusetts Medico-Legal Society will be held at the Hotel Statler, Boston, on Wednesday, May 17, at 2:30 p.m.

PROGRAM

Business Meeting.
Election of Officers.
Experiences of a Medical Examiner. Timothy Leary, M.D.

AMERICAN ORTHOPAEDIC ASSOCIATION

The sixty-third annual meeting of the American Orthopaedic Association will be held at the Cavalier, Virginia Beach, Virginia, from May 23 to 26, preceded by a Clinical Day in Baltimore on Monday, May 22. Dr. Robert W. Johnson will be president of the meeting.

NEW ENGLAND HEALTH INSTITUTE AND MASSACHUSETTS PUBLIC HEALTH CONFERENCE

A joint meeting of the fourth annual Massachusetts Public Health Conference and the New England Health Institute will be held at the University of Massachusetts, Amherst, on June 14, 15 and 16. The general sessions will include discussions on alcoholism, sanitation and the public health, public-health budgeting, and what most women want from public health. Section meetings of special interest will deal with the problems of health officers, maternal and child health, nutrition, health education, public-health nursing, laboratories and sanitation.

INTERNATIONAL ACADEMY OF PROCTOLOGY

The second annual convention of the International Academy of Proctology will be held at the Bellevue Hotel, San Francisco, California, June 23 and 24. The annual banquet will take place on Friday evening, June 23.

Further information concerning the convention and a copy of the program may be obtained from the Secretary, Dr. Alfred J. Cantor, International Academy of Proctology, 43-55 Kissena Boulevard, Flushing, New York.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

MAY 14–19. International and Fourth American Congress of Obstetrics and Gynecology. Page 160, issue of January 26.

MAY 16. The Springfield Hospital. Page 640, issue of April 20.

MAY 16. Harvard Chapter of Alpha Kappa Kappa. Notice above.

MAY 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

MAY 17. Luncheon Meeting. Section on Diseases of the Eye, Ear, Nose and Throat, Massachusetts Medical Society. Hotel Statler, Boston, 12:00 m.

MAY 17. Massachusetts Medico-Legal Society. Notice above.

MAY 18. The Springfield Hospital. Page 640, issue of April 20.

MAY 18. Boston City Hospital House Officers' Association. Page 735, issue of May 4.

MAY 20. The Springfield Hospital. Page 640, issue of April 20.

MAY 22 AND 23. National Research Council Committee on Human Reproduction. Page 488, issue of March 23.

MAY 23 AND 24. American Laryngological Association. Page 736, issue of May 4.

MAY 23–26. American Orthopaedic Association. Notice above.

MAY 24. New England Pediatric Society. Page 736, issue of May 4.

MAY 24–26. American Association of Genito-Urinary Surgeons. Page 234, issue of February 9.

JUNE 12–14. American Neurological Association. Page 600, issue of April 13.

JUNE 13. New England Society of Anesthesiologists. Page 735, issue of May 4.

JUNE 14–16. New England Health Institute and Massachusetts Public Health Conference. Notice above.

JUNE 22–25. American College of Chest Physicians. Page 270, issue of February 16.

JUNE 23 AND 24. International Academy of Proctology. Notice above.

JUNE 24 AND 25. American Society for the Study of Sterility. Page 38, issue of January 5.

JUNE 24 AND 25. American Academy of Dental Medicine. Page 640, issue of April 20.

JUNE 26–30. American Physicians Art Association. Page 428, issue of March 16.

JUNE 26–30. American Medical Association. Annual Session. San Francisco, California.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

AUGUST 28–SEPTEMBER 1. American Congress of Physical Medicine. Page 428, issue of March 16.

AUGUST 31–SEPTEMBER 7. World Federation for Mental Health. Page 306, issue of February 23.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

OCTOBER 12–14. American Association of Blood Banks. Page 428, issue of March 16.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

JANUARY 31. American Academy of Orthopaedic Surgeons (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MAY 18

FRIDAY, MAY 19

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

MONDAY, MAY 22

*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, MAY 23

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, MAY 24

*11:00 a.m.–12:00 m. Medical Rounds. Children's Medical Center.

*12:00 m. Clinical Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic of all Medical Center Services. Amphitheater, Children's Hospital.

*Open to the medical profession.